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OVERSIGHT ON TREATMENT OF ALZHEIMER'S DISEASE, 1983

HEARING

BEFORE THE

SUBCOMMITTEE ON AGING

OF THE

COMMITTEE ON LABOR AND HUMAN RESOURCES UNITED STATES SENATE

NINETY-EIGHTH CONGRESS

FIRST SESSION

TO EXAMINE THE PROGRESS MADE IN THE TREATMENT OF ALZHEIMER'S DISEASE, FOCUSING ON FEDERALLY FUNDED RESEARCH ON THE CAUSES, DIAGNOSIS, AND TREATMENT OF THE DISEASE

~~JUNE 28~~, 1983

May 16

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OVERSIGHT ON TREATMENT OF ALZHEIMER'S DISEASE, 1983

MONDAY, MAY 16, 1983

U.S. SENATE,
SUBCOMMITTEE ON AGING,
COMMITTEE ON LABOR AND HUMAN RESOURCES,
Washington, D.C.

The subcommittee met, pursuant to notice, at 10:09 a.m., in room SD-430, Dirksen Senate Office Building, Senator Charles E. Grassley (chairman of the subcommittee) presiding.

Present: Senators Grassley and Denton.

OPENING STATEMENT OF SENATOR GRASLEY

Senator GRASSLEY. Today's hearing begins the first in a series of discussions to be conducted by this subcommittee on topics related to the health and welfare of the elderly.

Aging has long been mistakenly associated with declines in both mental and physical functioning. A generation ago, almost anyone over the age of 65 who experienced marked confusion, or disorientation, and loss of memory was said to have hardening of the arteries, a condition thought to be inevitable, progressive and incurable.

We now know that aging and deterioration of these functions are not synonymous and furthermore, that many persons enter their seventh, eighth, and ninth decades of life with no measurable decline in their intellectual abilities.

Until the present, Alzheimer's disease has been a little-known but surprisingly common disorder that affects the cells of the brain. The disease produces intellectual impairment in 1.5 to 2 million American adults. While experts formerly believed that Alzheimer's disease occurred most often in persons under age 65, this disorder is now recognized as the most common cause of severe intellectual impairment in older adults.

This illness is ranked as the Nation's fourth-leading killer, responsible for an estimated 100,000 to 120,000 deaths a year just in the United States. It generally reduces a person's normal life expectancy by one-half.

Family members care for the majority of demented and frail individuals in their homes. Unlike cancer or stroke or any number of maladies, Alzheimer's disease is usually not physically debilitating in its early stages. Nevertheless, the victim needs a constant caretaker—"constant" means 24 hours a day, since one of the characteristics of the disease is a restlessness that leaves the victim unable to sleep and causes him or her to wander aimlessly. Often,

family members speak of their afflicted wives or husbands or parents in the past tense and they agonize over not being recognized, or their feeling that a stranger has inhabited the body of a loved one.

In 1979, the annual cost of nursing home care for persons with Alzheimer's disease was approximately $6 billion or one-half of the cost of all nursing home care for the elderly in that year. It is estimated that these costs will rise to $30 billion by the end of the 1990's.

In the past decade, scientists around the world have made great progress in the understanding of Alzheimer's disease. Recently, scientists reported some promising results with a drug that potentially improves memory of persons afflicted with the disease.

We are encouraged to hear that our first witness, Mrs. Margaret Heckler, Secretary of the U.S. Department of Health and Human Services, has pledged that her Department will give top priority to research on this disease. We are very honored that this is Secretary Heckler's first appearance at a hearing in Congress.

Accompanying the Secretary are Dr. William E. Mayer, Administrator of Alcohol, Drug Abuse, and Mental Health Administration, and Dr. James B. Wyngaarden, Director of the National Institutes of Health.

I welcome you, Madam Secretary, and before you begin, I would like to point out for other people who have read the roster of people who are testifying today that Senator Pressler is unable to testify due to a scheduling conflict, and he did leave testimony that I will have inserted in the record without objection, and Senator Hatch, who is also on the agenda, plans to join us as soon as he can. He had another speech to give this morning. I also would like to compliment Congresswoman Olympia Snowe, who is author of a bill dealing with this matter, H.R. 2857. She could not join us this morning, and she also has a statement for the record that I will incorporate.

[The opening statement of Senator Hatch follows:]

Opening Statement of Senator Hatch

Senator Hatch. Good morning, I am pleased to be participating in this subcommittee hearing on Alzheimer's disease. I want to commend Senator Grassley for holding this hearing to focus on this condition, which affects not only middle-aged individuals, but a sizable proportion of our elderly population. This tragic illness gradually robs its victims of their memory, and eventually of all intellectual function.

Alzheimer's disease is the most common form of senile dementia and affects 5 percent of the over-65 population, 20 percent of the over-80 population, and indications are that the risk of having the disease continues to increase dramatically the longer a person lives. During the course of this hearing, we will be provided with an overview of federally funded research on what causes Alzheimer's disease, how to treat it, and how we might someday be able to prevent it.

Because of the gradual onset and progress of Alzheimer's disease, it is a long-term debilitating condition which takes its toll not only

on the victims, but their families, and ultimately society at large. It causes great economic demands and is responsible for many of the attitudes and much of the stereotyping of the elderly. While the disease is not initially life-threatening in the strictest sense of the word, it shortens life expectancy and severely impinges on the quality of the lives of the 1.5 million to 2.5 million people it affects. More than any other disease associated with aging, it compromises the ability of its victims to maintain their independence. The tremendous emotional and financial burden of care for the Alzheimer patient typically falls on an elderly spouse, or children who are themselves growing older. Even when there are ample financial and other resources, Alzheimer victims often spend their last days in institutions.

In economic terms, Alzheimer's disease is a major contributor to the annual cost of chronic care for the elderly population. In 1980, $22 billion was spent on nursing home care; by 1990, given the increasing numbers of elderly, particularly in older age groups, that cost will approximate $75 billion. If current estimates related to the numbers of patients with dementia (dee-men-sha) in nursing homes stay the same, between one-third and one-half of the cost of this care will be attributed to Alzheim victims.

I look forward to hearing the testimony of Mrs. Margaret Heckler, who, in her short time as Secretary of the Department of Health and Human Services, has demonstrated her concern for the needs and problems of the growing number of elderly Americans. I am also pleased to see the leaders of each of the Federal Government's eminent scientific institutes which share an interest in research related to Alzheimer's disease. Once thought to be a hopeless and an inevitable affliction, senile dementia has received considerable attention from the scientific community in the last decade, largely due to the leadership and the staff of the organizations represented here today.

The public's awareness of the tremendous and perhaps unnecessary suffering caused by senile dementia continues to grow. Not a week goes by that we don't see some newspaper or magazine article related to this disorder. It is my hope that during this hearing these expert witnesses will help us to better understand recent scientific research, and provide us with insights into how we may soon be able to treat and ultimately prevent one of the cruelest disorders associated with old age.

[The prepared statements of Senator Pressler and Congresswoman Snowe follow:]

Prepared Statement of Hon. Larry Pressler, a U.S. Senator
from the State of South Dakota

Mr. Chairman and Members of the Subcommittee -

I would like to begin by thanking you for the opportunity to appear before the Subcommittee today.

Of course, I have a deep personal interest in the matter of Alzheimer's disease, but I also believe that it is in our national interest, as well, to put a halt to this terrible illness.

Mr. Chairman, for a variety of reasons Alzheimer's disease has to be regarded as one of the most serious threats to this country's health and well-being.

- First and foremost is the fact that more than 2 million persons suffer from Alzheimer's disease; an estimated 120,000 persons die each year as a consequence.

- Second, consider the fact that this disease now costs society more than $26 billion annually for nursing home stays and in-home care.

- Finally, consider, too, the prospects for the future. The experts predict that in 40 years there will be 43 million Americans age 65 and

over -- or nearly double today's elderly population. This, Mr. Chairman, is the age group that is most vulnerable to Alzheimer's disease.

All things considered, we may face a serious hemorrhaging of our society unless we do more to combat Alzheimer's disease.

The way to prevent this from happening is by finding a cure or treatment for the disease. That can only come through research -- high quality, sustained research -- and the full support of the federal government.

I, like many of my colleagues, were pleased to learn of the high priority Secretary Heckler has assigned to this area. This sort of commitment, together with adequate resources at the NIH, are essential.

At the same time, Mr. Chairman, we cannot turn our backs on those who are already enduring the illness, anxiety, and even want that accompanies Alzheimer's disease. Nor can we overlook the sobering fact that even more people will be afflicted with Alzheimer's before researchers can come up with an answer.

I think it is time we take a good hard look at what is going on right now and begin to address the needs of the patients and their families.

Diagnosis and Treatment Services

To begin with, there needs to be a much greater emphasis on informing physicians of the latest information we have on Alzheimer's disease. Whatever knowledge that is accumulated through research will be of little value unless it is passed on to those who need to use it. Along these lines we must ensure that health professions schools, nursing homes, and medical associations keep medical personnel abreast of the latest developments in the diagnosis and treatment of the disease. At the same time, regional referral systems ought to be established to help aid in the diagnosis and treatment of more difficult cases of this disease.

Patient and Family Services

Mr. Chairman, many families would prefer to care for their loved ones at home rather than seek more costly care through nursing homes. The problem is that Alzheimer's patients oftentimes require around-the-clock care and attention.

We can make that choice between home and institution an easier one by promoting greater emphasis on home health care and adult day care.

At the same time, we should extend to these families the sorts of services that are now provided through the Administration on Aging, and its state and local counterparts. Here I am speaking of such services as homemaker aides, transportation, in-home respite care, and nutrition.

Care for Veterans

Still another concern involves the treatment of veterans with Alzheimer's disease.

Over the next 20 years, Mr. Chairman, the proportion of veterans in that vulnerable over-60 age bracket will triple. Yet the Veterans' Administration has no uniform, nationwide policy with respect to Alzheimer's patients. What that means is that while some Alzheimer's patients are admitted to VA nursing homes -- others are turned away.

Mr. Chairman, these are the sorts of issues confronting us today. Unfortunately, families cannot even turn to Medicare or their own insurance plans for help. That is why I believe we have a responsibility to help.

So that there is no misunderstanding, I am not advocating that the government take on full responsibility. On the contrary, this is a national problem and it requires a national effort involving not just government but individuals and families, state and community agencies, private industry, and labor.

Mr. Chairman, this country has come a long way in this century. Medical science has enabled us to extend the average life span by more than 20 years. But, unfortunately, what the historian Toynbee called "the last of life, for which the first was made..." is still not a golden age for many of our citizens.

At this point, I would like to place in the record a document which I requested from the Alzheimer's Disease Association. It addresses some of the issues I raised with the Subcommittee today and I believe it deserves our careful consideration.

Thank you, Mr. Chairman.

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and Related Disorders Association, Inc.
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May 11, 1983

Honorable Larry S. Pressler
United States Senate
SR 415 Russell Building
Washington, D.C. 20510

Dear Senator Pressler:

At your request, I am enclosing a copy of our proposed National Program to Conquer Alzheimer's Disease.

Without a doubt, this Nation has built an extraordinary health record. Life expectancy has been increased by more than 20 years since the start of this century. The array of new treatments, modern drugs, and medical techniques have contributed significantly to the extension of life. But each breakthrough enables us to concentrate more on the remaining dangers.

Certainly, Alzheimer's disease must be regarded as one of the most serious threats to the Nation's health and well-being.

Today, more than 2 million persons suffer from Alzheimer's disease. While most are over 60, between 15 to 20 percent of the victims are younger. As it stands now, Alzheimer's disease results in 120,000 deaths each year, making it the fourth leading killer among the adult population.

As a result, what was once termed "the silent epidemic" is fast becoming a very visible source of concern to the public, the medical community, and the government. This growing concern stems in large measure from the fact that so many people have already fallen victim to the disease and the realization that soon, more people than ever before will fall within the vulnerable over-60 age group. Compounding the problem is the fact that the loss of valuable human resources will result in substantial added costs to society. Already, more than $26 billion is spent annually to care for Alzheimer's patients.

The sobering fact is that our remarkable scientific achievements prolonging the lifespan, for many, will mean added years filled with illness and anxiety.

Senator Pressler

Our Association is appreciative of all of the work you and your colleagues in the Congress have devoted to promoting greater national awareness of Alzheimer's disease. We also commend Secretary Heckler for taking steps to ensure that research on this dread disease is given the highest priority.

Certainly, there is still much more to be done, for the challenge we face with Alzheimer's disease is a serious and far-reaching one. This is a national need and it requires a national effort involving not just government but individuals and families, states and communities, professional and voluntary groups, and private industry. This national effort must be comprehensive in scope and coordinated in its approach to the myriad of problems associated with Alzheimer's disease.

Todward this end, the Alzheimer's Disease and Related Disorders Association has prepared the attached National Program to Conquer Alzheimer's Disease. The program was prepared by the Association, with valuable input from families, research specialists, physicians, and government experts and is intended to respond to the most pressing needs of both the victims and their families. The two primary objectives of the program are to (1) promote research on finding a cure and treatment and (2) assist those who presently suffer from the disease.

Since its inception, our Association, through its 68 member chapters and 300 family support groups, has devoted itself to encouraging greater awareness of this catastrophic illness. In so doing, the Association hopes to stimulate others to begin addressing the serious issues surrounding Alzheimer's disease. It is in this spirit that the attached program was prepared and is now being presented.

We encourage you to use these materials as a guide in the formulation of public policy. We are prepared to provide you with whatever additional assistance you may need.

Sincerely,,

Jerome H. Stone
President

BIOMEDICAL RESEARCH SUPPORT

Research is a primary requirement in the battle against Alzheimer's disease. This country must invest in high quality research on the prevention, treatment and restoration of lost function associated with Alzheimer's disease. This will require a far greater degree of support and attention to the problem by government, research institutions, and independent investigators throughout the country.

Federal Support

Clearly, the federal role in medical and health-related research is a substantial one. Research on Alzheimer's disease is now being minimally carried out through a number of government agencies including the National Institutes of Health (NIH), the National Institute of Mental Health (NIMH), and the Veterans' Administration (VA).

While the cause of Alzheimer's disease still remains a mystery, research supported by these agencies has began to produce some promising leads. It is therefore recommended that funding for research relating to Alzheimer's disease be assigned a high priority by government and that the following actions be taken to help complement a national research effort:

- Interagency Coordinating Committee - In order to make the most of the federal research investment, an interagency committee should be established for the purpose of coordinating research throughout the federal government, and reporting annually to the President and the Congress on the level of government investment, significant research findings, priority areas of research, and requirements for future funding.

- Nongovernmental Research - Research support should not be limited to government agencies. Since Alzheimer's disease is a national concern, others must share the responsibility for finding answers to the problem. These include private industry, insurance companies, foundations, and pharmaceutical houses. To this end the Alzheimer's Disease and Related Disorders Association has, with its limited resources, initiated a research grants program. The Association is encouraging private sector participation in this endeavor.

- Information Clearinghouse - The accumulation of knowledge through research is of little value unless communicated in useful form to those who need to use it -- to other scientists, educators, practitioners, administrators, and the public. Improved scientific communication regarding Alzheimer's disease is an urgent goal. A government-operated clearinghouse should be established and should immediately put in place systems for making available more health research results and information on Alzheimer's disease.

PATIENT CARE AND FAMILY SERVICES

The delivery of services to Alzheimer's patients and their families must be improved, particularly in the following areas:

- Diagnosis and Treatment - Research is now underway to help develop more clear-cut methods for diagnosing Alzheimer's disease. In the meantime, efforts should be undertaken to ensure that persons who may now be suffering from the disease are properly diagnosed. Strong emphasis must also be placed on informing physicians of the latest modalities of care. Minimally, health professions schools, medical organizations, and professional associations should undertake to keep medical personnel abreast of the latest developments in the diagnosis and treatment of Alzheimer's disease.

  It is the intent of the Alzheimer's Disease and Related Disorders Association to work with the American Medical Association, the American Society for Internal Medicine, the American College of Physicians, the American Nursing Association, and others to establish in-service training programs and support medical and scientific conferences throughout the country.

  Schools of medicine, nursing, and allied health professions should all be encouraged to include Alzheimer's disease

in their continuing education and training programs. The Department of Health and Human Services should support curriculum development activities in medical, osteopathic, and nursing schools.

Also, regional referral systems ought to be established to help in the diagnosis and treatment of more difficult cases.

- Home Care/Adult Day Care - Many Alzheimer's patients, particularly those experiencing the early stages of the disease, are cared for by their families, most often the spouse. But because patients often require around-the-clock care and attention, many families are forced to seek more costly institutional care for their loved ones.

  To afford families a choice between the home and an institutional setting should be a matter of high priority. Toward this end, the federal government should promote greater emphasis on home health care and adult day health care for Alzheimer's patients. State and local institutions should, of course, play an active role in this endeavor.

- Community Services - Families (particularly spouses) of Alzheimer's patients are in need of a variety of services such as homemaker aides, transportation, residential repair, in-home respite care, and nutrition. State agencies and community-based organizations should extend these services

to the families in need. Federal agencies such as the Administration on Aging should seek to eliminate any restrictions which may now limit access to services.

- Care and Treatment for Veterans - Today, approximately 10 percent of the veteran population is over age 60; by the year 2000, the proportion of veterans in that vulnerable over-60 age bracket will exceed 30 percent.

  Despite the fact that increasing numbers of veterans with Alzheimer's disease are seeking help, the Veterans' Administration has no uniform policy in this area. While some veterans with Alzheimer's disease are admitted to VA facilities, others are turned away. The VA should immediately implement a consistent national policy affording these veterans access to appropriate VA care.

The overarching problem, it should be noted, lies in the absence of an integrated care continuum for Alzheimer's patients. All to often, family care givers receive little help in administering medications or in preparing for the transition from home care to institutional care. Furthermore, physicians frequently move the patient from provider to provider without linking together the total health care needs of the patient.

New models need to be developed to tie in the various health care providers, including institutions. Special care must also be

devoted to protecting the rights and dignity of patients.

Also of particular concern to families of Alzheimer's patients is the accessibility of high quality nursing home care. It is recommended that nursing home personnel receive more adequate training about Alzheimer's disease and that appropriate standards of care be established and adhered to.

MEDICAL AND FINANCIAL ASSISTANCE

Virtually all of the costs associated with the care and treatment of Alzheimer's patients are borne by the spouse or other family members. Medicare does not cover this illness, nor do most private insurance plans. Medicaid, on the other hand, will cover some of the costs incurred, but only if family resources have been exhausted.

Medicare, Tax Credits, and Alternative Approaches

As in the case of biomedical research, the federal government must assume lead responsibility in this area. In weighing the overall (and projected) social and economic costs, the government should give consideration to extending Medicare benefits to victims of Alzheimer's disease. At the same time, the government should examine the prospects for alternative financing and reimbursement mechanisms -- such as tax credits for home health care and reimbursement for hospice care -- which best correspond to the needs of the Alzheimer's patients and their families. It is also recommended that the National Center for Health Services Research act as lead agency in formulating and coordinating the government's health services research activities in this area. The Center should support research which focuses on alternative approaches for delivering care to Alzheimer's patients, and seek organizational and payment methods which reduce costs without adversely affecting quality.

Disability Coverage

The federal government should also examine the Disability

Insurance program with a view towards extending coverage to workers disabled as a result of Alzheimer's disease.

Pension and Insurance Plans

Some responsibility falls to private industry and labor organizations. Both should review their pension plans and insurance arrangements and extend appropriate coverage to meet at least a portion of the expenses associated with Alzheimer's disease.

Olympia J. Snowe

OLYMPIA J. SNOWE, M.C.

TESTIMONY OF OLYMPIA J. SNOWE

ALZHEIMER'S DISEASE
SENATE SUBCOMMITTEE ON AGING
MAY 16, 1983

Mr. Chairman:

I commend your efforts for holding this hearing which focuses on the progress made in the treatment of Alzheimer's disease, perhaps today's most misunderstood affliction of the elderly.

It is heartening to know national attention is now being directed towards identifying the proper diagnosis and possible cures of Alzheimer's disease. The House Select Committee on Aging, of which I am a member, has scheduled its own hearing on Wednesday, May 11, to examine possible causes of Alzheimer's disease. The public and the Congress have only just recently become aware of the fact that Alzheimer's disease is an illness of the brain and not a normal consequence of aging. As a disease, it would be preventable and treatable.

During the past several years, as the medical community found cures for illnesses that resulted in drastically shorter lifespans, we discovered "new" afflictions which were actually prevalent but were not common or understood. There were fewer of us left to manifest these diseases of middle age or later years. Now we know that the heretofore almost unknown illness, Alzheimer's disease, will affect 1 out of 6 of us and is the fourth leading cause of death. These statistics are impressive enough, but it almost defies the imagination to project the related human suffering over the next two or three decades as our aging population increases.

From reports just recently published by the medical community and government agencies, the future looks hopeful. A discernible area of the brain appears to be the focus of Alzheimer's disease in its early stages. Certain biochemicals necessary for neuron transfer have been found missing or critically reduced. Drugs which may modify the disease's progress are now being identified and produced. Coordinated research efforts and adequate funding should certainly enhance the possibility of identifying the exact causes and cures soon.

The testimony to be offered today will help guide those of us in Congress in assisting the medical community in its Alzheimer's disease research efforts. I have introduced legislation in the House of Representatives with that hope in mind. I look forward to the comments of the medical community today and at the House Aging Committee hearing on Wednesday to determine the best course of Federal action which would enhance the research activities within government agencies and the private sector. Again, Mr. Chairman, thank you for taking the initiative on this most important issue.

Senator GRASSLEY. Welcome, Secretary Heckler. We appreciate very much your willingness to take out of your busy schedule the time necessary to help us with this, but I also want to compliment you for your leadership, as demonstrated by your first news conference, in which you spoke of this issue as well.

Thank you, and proceed.

STATEMENT OF HON. MARGARET M. HECKLER, SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES, ACCOMPANIED BY DR. WILLIAM E. MAYER, ADMINISTRATOR, ALCOHOL, DRUG ABUSE AND MENTAL HEALTH ADMINISTRATION, AND DR. JAMES B. WYNGAARDEN, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

Secretary HECKLER. Thank you, Mr. Chairman, and members of the committee.

I come to join with you this morning on a very important rescue mission because the disease which is on our agenda today, Alzheimer's disease, literally sets millions of Americans adrift on a sea of lost memory, lost contact with those who love them, lost grip on their own lives.

Alzheimer's disease dulls the mind and kills the memory. It takes our loved ones from us almost as painfully as death itself. Every breakthrough we achieve, every advance we make in our research into the causes, diagnosis, and treatment of Alzheimer's disease, is a step toward literally, the reuniting of families and friends; the lifting of a veil of confusion and isolation from Americans who deserve days and years of celebration in their final years, not days and years of drift, which is the sentence Alzheimer's disease imposes.

Promising research into the causes, diagnosis and treatment of Alzheimer's disease is ongoing through the efforts of the research institutes within the National Institutes of Health and the Alcohol, Drug Abuse, and Mental Health Administration.

Accompanying me today, Mr. Chairman, are the heads of these agencies—Dr. William Mayer, Administrator of ADAMHA, and Dr. James Wyngaarden, Director of NIH. Also present are the directors of the three principal institutes focusing on the medical and research aspects of Alzheimer's disease: Dr. Murray Goldstein, Director of NINCDS, Dr. Herbert Pardes, Director of NIMH, and Dr. Robert L. Ringler, Acting Director of NIA.

At the outset, Mr. Chairman, I want to express, on behalf of the administration and all of us concerned with the health and well-being of the elderly, our appreciation for the attention you and the members of this subcommittee are focusing on the problems of aging. The problems of our elderly Americans is one of my highest priorities as Secretary of HHS. Thus, Alzheimer's disease also is a priority concern.

It is a surprisingly common disorder that affects the cells of the brain. While experts formerly believed that Alzheimer's disease only occurred in persons under 65, this disease is now recognized as the most common cause of severe intellectual impairment in older Americans.

Our focus this morning will be on Alzheimer's disease in the elderly, and it is indeed a disease of catastrophic proportions. It affects at least one in every 20 people between 65 to 75 years of age, and two in every 10 over 80 years old. Alzheimer's disease is the cause of serious confusion and forgetfulness—serious forgetfulness—in some 1.5 million to 2.5 million elderly persons in the United States. It is also one of the major reasons so many elderly people end up in nursing homes—as many as one-half of the more than one million elderly in long-term care facilities are afflicted with Alzheimer's disease. The present cost to the Nation of nursing home care for these patients is estimated to exceed $12 billion each year.

Further, because of the decrease in life expectancy accompanying this illness, Alzheimer's disease is thought to be the fourth leading cause of death among adults over age 65. Generally, from the time of onset, the disease reduces a person's remaining life expectancy by about one-half. Most people die of the accompanying complications within 8 to 10 years of onset. It is responsible for the deaths of some 120,000 Americans each year.

The major debilitating symptoms of Alzheimer's include serious forgetfulness, particularly about recent events, and very serious confusion. At first, there are only minor and almost imperceptible symptoms, often attributed to emotional disturbances or other physical illnesses. Gradually, however, the afflicted man or woman becomes more forgetful. They may neglect to turn off the oven, forget how to balance a checkbook, forget how to play their favorite card game. Often, they become irritable, restless and agitated. Over the course of a few years, they lose the ability to use their hands for writing, cooking and dressing. Eventually, they have difficulty with speaking and understanding language. Even when a loving and caring family is available to give support, the victim of Alzheimer's is very likely to spend his or her last days in a nursing home.

While my words can graphically describe numbers and facts, they cannot adequately outline and detail the human cost, the tragedy of this disease. In a recent New York Times magazine section article, one of the Times news assistants, Marion Roach, told the story of her family's losing battle with Alzheimer's disease. She told the story about her mother, a beautiful, intelligent woman, a college graduate, a schoolteacher, a woman who loved her family. In 1979, she became an Alzheimer's disease statistic. Within months, she became forgetful, disoriented. She forgot what day it was, she abruptly hung up the telephone on her friends. Now, she repeats the same few questions and stories over and over again, unable to remember she asked the same question or told the same story only a few minutes before. She now spends most of her days staring at the television—without the sound turned on. As her daughter put it simply, "My sister and I are angry. We are angry that our mother is 54 and losing her mind."

At the present time there is no established treatment that can cure, reverse, or stop the progression of this tragic disease. However, national and international interest in studies on the cause and treatment of senile dementia has been rising dramatically. Since 1976, HHS research activities on the dementias of aging have

increased by more than 500 percent, and the increased attention has resulted in growing cooperation and coordination among the Federal research institutes responsible for studies on aging, neurological disorders and mental health. For example:

Over the years, cooperative efforts among the National Institute on Aging, the National Institute of Neurological, and Communicative Disorders and Stroke, and the National Institute of Mental Health have led to the sponsorship of a variety of important national and international conferences on the prevalence, causes, and possible treatment of Alzheimer's disease, on the diagnosis of dementia in its curable and incurable forms, and on the ethical implications of research on patients whose capacity to speak for themselves has been compromised.

One particularly successful cooperative venture of the Institutes, a meeting of self-help family support groups, was the foundation for the formation of the Alzheimer's Disease and Related Disorders Association. Since 1979, this organization has grown to include more than 60 chapters and 300 family support groups. In addition to offering counsel and support to affected families, it gives small grants to young investigators and investigators new to the field, and it educates members about the need for research and for definitive diagnosis of the disease.

Currently, NIA, NIMH and NINCDS scientists are involved in a study of cerebrospinal fluid concentrations possibly involved in normal aging and dementia. In a second study, NIA and NIMH scientists are collaborating in a study to assess motor coordination and motor function in healthy aged persons and in individuals with dementia.

NINCDS has an interagency agreement with NIMH to provide information on the incidence and prevalence of Alzheimer's disease, the history and progression of the disease, and on the economic and social impact of the disease as it affects individuals, their families and their friends. In a similar study, NIA and NIMH are studying mental illness in general, and Alzheimer's disease in particular, in a community of 3,000 people who are over the age of 65.

We have reached outside the precincts of government for allies in the private sector. Major American corporations have been enlisted in the struggle. These joint efforts have been aimed both at advancing research in Alzheimer's disease and in educating physicians who care for Alzheimer patients. I have with me today examples of publications developed by the NIMH in partnership with the pharmaceutical industry and other corporations, notably AT&T, now American Bell. These two publications—the "Physicians Handbook on Psychotherapeutic Drug Use in the Aged," and "Strategies for the Development of an Effective Treatment for Senile Dementia"—have been distributed to over 150,000 physicians. Through such cooperative efforts with private industry, major advances may be expected in both research and in the treatment of this tragic disorder.

Less technical, but equally informative publications have been reproduced and widely distributed to the general public. This NINCDS publication, for example, provides information about dementias, including Alzheimer's disease, and this NIA fact sheet on the myths of senility has been distributed to more than one-half

million people across the country. This simple factsheet is very valuable on the subject and, I think, useful for the layman, as well as the physician. Across the country, this valuable question and answer booklet on Alzheimer's disease has been distributed by the Alzheimer's Association and the American Association for Retired People.

I will leave some here for you, Mr. Chairman, for the benefit of yourself and the committee.

Senator GRASSLEY. Thank you

Senator HECKLER. Major advances have been made in studies of aging and the brain. The increased interest and collaboration of the research institutes have established a solid foundation for research, which has improved our understanding of this disease.

We now know some of what goes wrong in the brain of persons with Alzheimer's disease. One or more of the chemicals that nerve cells use to carry messages from one nerve to another are greatly reduced, and specific cells deep within the brain die in these patients. Through research supported by HHS, we are trying to learn what causes these specific cells to die and will use this information to learn when and how to intervene, how to prevent and to treat this disease. The doors that have locked up the secrets of the "how's" and "why's" and "what's" of Alzheimer's disease have slowly begun to open. I am determined to speed that pace. That is why I have established a new departmental task force on Alzheimer's disease. I have asked the Assistant Secretary for Health, Dr. Edward Brandt, to chair the task force. The task force will coordinate and speed the intensive research already being done at HHS on Alzheimer's, pinpoint the most promising avenues for future research, and act as the vehicle to translate research findings into policy, programs and practical means for improving the quality of life for older Americans. The task force will also become an activist, ongoing mechanism for sharing information with other program heads in the Federal departments which serve the elderly, such as the Health Care Financing Administration and the Administration on Aging.

Already, the Veterans' Administration has asked to join the HHS task force. We welcome them as valued allies in our crusade. The task force met for the first time on April 28 and reviewed the status of current research and other activities being carried out by this Department and the Veterans' Administration. Our next meeting is already scheduled. It will develop a definitive program of action. I will be an active partner in the task force's work because I am determined that we will find a winning research strategy in the battle against Alzheimer's disease. There is no time to lose.

At present, 26 million Americans are age 65 or older. By July 1 of this year, experts predict that the United States will reach a new milestone. For the first time in this country's history, there will be more people over 65 than teen-aged. These groups will represent 11.7 percent and 11.3 percent of the population, respectively. In the year 2025, 19 percent of all Americans, 59 million people, will be over the age of 65. Because Alzheimer's disease is characteristically a disease of the aged, we can expect the number of its victims to grow and the cost of caring for them will also continue to grow. Estimates are that we will spend $40 billion or more each

year for nursing home care for Alzheimer's disease victims within just this decade.

I embrace Nobel Laureate's Simon Kuznets' wise words: "Demographics is destiny." The graying of America has profound implications for our country. It confronts us with very serious challenges, especially in the health field. This administration recognizes those challenges—total funding for research relevant to Alzheimer's disease which was $17 million in fiscal year 1981 will rise to a proposed $25 million in fiscal year 1984. These figures are a measure of our commitment that all Americans, whatever their income or personal circumstance, can grow older with human dignity.

I have no illusions about the difficulty of curing or preventing Alzheimer's disease. But, as one who has always had a deep concern about this problem, I am encouraged by the research, the energy, and the resources that we are devoting to the problem. I hope that we may look back upon this time as a turning point.

Thank you, Mr. Chairman. I would be pleased to answer any questions you may have.

Senator GRASSLEY. Before we go to questions, do either Dr. Wyngaarden or Dr. Mayer have anything that they wish to note?

Dr. WYNGAARDEN. No, Senator.

Dr. MAYER. No, sir.

Senator GRASSLEY. First, I want to thank you for your testimony. More importantly, thank you for your leadership in this area. And for all the people who are potential sufferers of this disease, I think we need to take our hats off to this administration in times of budget constraints in seeing the necessity for putting the money that they have into research of this disease. It is not only important for the well-being of those people and their families who are affected, but because of the cost of this disease, it will not be long before that small investment will be showing rewards, not only financial rewards, but a better life for people who are cured.

Madame Secretary, at your April 6 press conference, you discussed new advances made in treatment of Alzheimer's disease through the use of two drugs. Would you tell us about those advances?

Secretary HECKLER. The advances relate to promising research done at different locations on the subject of Alzheimer's disease. They each use drugs currently available; naloxone and physostigmine. The early data have been very interesting. We are, of course, a long way from establishing a definitive treatment for the disease. However, the investigations show that there is promise and the possibility that the disease may be modifiable. I think that the initial gains have provided a sense of hope on the part of the researchers in the development of a therapy through two different approaches. While these will need to be substantiated in further experiments and in further treatment samples, the preliminary findings show the possibility that there can be a reversal of the symptoms of the disease. This affords great hope on the part of the researchers and our Department.

Senator GRASSLEY. Is HHS carrying out any studies that examine the role of the family in the treatment of Alzheimer's patients? Is funding authorized under medicare for long-term custodial care?

Secretary HECKLER. The role of the family, is of critical importance. Our Department has several innovative new studies in progress, which are aimed at understanding the options and the problems confronting the family with an Alzheimer's member, as well as approaches that can be taken to enhance family skills. Other research is underway to evaluate the differential efficiency of family and group counseling and the counseling of support groups and caregivers. As you can see, we do have studies underway which deal with the family support mechanism. On the issue of reimbursement, I understand that most insurance plans, including medicare, will reimburse for the diagnostic or differential diagnostic workup of a patient suspected of having Alzheimer's disease. However, medicare and other insurance reimbursement appears to end as the approach to managing the Alzheimer's patient becomes one of custodial care. Most insurance plans do not reimburse for custodial care.

With regard to home care, we have somewhat the same situation. Most insurance plans will not pay all the needed services, since they are considered custodial or support services rather than skilled services.

The economic burden on families continues to be a source of great concern. This issue has been placed on the agenda of the Department and of the task force formed to deal with the whole issue of Alzheimer's disease. The task force will be looking at the problem in depth and in their final report, they will address this issue, along with others. I will be happy to share this information with you when this report is submitted, Mr. Chairman.

Senator GRASSLEY. I believe you clarified in your statement the amount of money that your Department is actually spending on research in Alzheimer's disease. Seventeen million dollars was allocated for the current year, projected to go up to $25 million for the next year; is that right?

Secretary HECKLER. No; $17 million in 1981; $20,353,000 in 1982; and $22,340,000 in 1983, projected to go to $25,710,000 in 1984. This reflects a proposed 12-percent increase from 1983 to 1984. We believe this is a substantial increase.

Senator GRASSLEY. Senator Denton wondered how that money was being disbursed in the way of research. Can you give us any clues as to the agencies, both private sector and governmental, that are spending that money?

Secretary HECKLER. I can give you some information on it. For NIH, the 1983 estimate is $15,312,000, of which $8,109,000 is in clinical research. That figure is proposed to increase to $10,025,000 in 1984. The estimated expenditure for behavioral studies at NIH is $643,000 in 1983; $747,000 is proposed for 1984. The total NIH expenditure for research directly related to Alzheimer's disease is estimated to be $15,955,000 in 1983; and $18,597,000 is proposed for 1984. In addition, it is estimated that NIH will spend $17,390,000 in 1983 for research indirectly related to Alzheimer's disease; $20,117,000 is proposed for 1984. At ADAMHA, the estimated expenditure for 1983 is $4,950,000 and $5,600,000 is proposed for 1984. I would be happy to submit a more detailed breakdown for the record, Mr. Chairman.

Senator GRASSLEY. Yes, we would appreciate it if you would do that.

[The tables referred to follow:]

NATIONAL INSTITUTES OF HEALTH

Alzheimer's Disease
(Dollars in thousands)

	1982 Actual	1983 Estimate	1984 Estimate
Directly Related, NIH			
Biomedical	$13,715	$15,312	$17,850
(Clinical)	(6,968)	(8,109)	(10,025)
Behavioral	582	643	747
Subtotal	14,297	15,955	18,597
Indirectly Related, NIH			
Biomedical	1,256	1,435	1,520
Subtotal, NIH	15,553	17,390	20,117
Subtotal, ADAMHA	4,800	4,950	5,600
TOTAL, PHS	20,353	22,340	25,717

NIMH
Budget Figures on Alzheimer's Disease
(Dollars in Thousands)

	FY82 Actual	FY83 Proposed	FY84 Requested
Extramural	$ 4,100	$ 4,200	$ 4,800
Basic[1]	(1,230)	(1,260)	(1,440)
Clinical[2]	(2,870)	(2,940)	(3,360)
Intramural	700	750	800
Total	$ 4,800	$ 4,950	$ 5,600

[1]Basic research includes preclinical and clinical drug approaches.

[2]Clinical research includes biomedical, behavioral, and psychosocial approaches.

Senator GRASSLEY. I want to recognize Senator Denton from Alabama, who has joined us at this hearing. Since he had aging as part of the subcommittee which he now chairs, during the 1981 and 1982 sessions of the Senate, I think that speaks for his interest in the health and welfare of the elderly. His present subcommittee has jurisdiction over many programs dealing with the elderly, like the action program and senior companion programs. Just as soon as I am finished asking a few more questions, I will call upon you for a statement and also to question Secretary Heckler.

Mrs. Heckler, during markup of the National Institute of Health reauthorization bill before the Labor Committee, an amendment was adopted that provides for the establishment of an interagency task force on Alzheimer's disease and authorizes appropriations of $4 million for Alzheimer's disease research. I understand that the task force you have established is fundamentally identical to that in the amendment, and therefore, that portion of the amendment has already been accomplished.

I would like to have a verification of that, and then, could you also tell me your views on the $4 million research earmark in that bill, as well?

Secretary HECKLER. Mr. Chairman, our task force has been established—it was initially an HHS task force, pulling together both the programs and institutes representing the research efforts of HHS, as well as the components involved in the programmatic areas of the elderly and aging. Subsequently, after the introduction of our task force and its founding, the Veterans' Administration on their own initiative asked to join the task force. They are now a member of the task force and we are delighted to have them. I think this task force could very well be characterized as an interagency task force. Therefore, I think mandating such a task force legislatively is absolutely not necessary.

Senator GRASSLEY. Do you have any comment on that $4 million research that was earmarked in the bill?

Secretary HECKLER. In general it is the feeling of NIH—and I think, very appropriately—that limitations on their flexibility are both unwise and unnecessary. I think that we nonscientists have to appreciate the difficulties that they face when we earmark funds even for the most desirable cases. We reduce the flexibility of our research institutes to respond and to pursue the most fruitful avenues of research. Often, the answers to a particular disease do not result from research that is directed just to that disease, but may come from other areas. For example, research on neurotransmitters and on memory function provide the essential bases for the targeted effort on Alzheimer's disease.

Another example is the progress which is now being made in AIDS because of research already underway related to viruses immunology. I think that the scientists are indeed correct in that they must develop a scientific basis of knowledge through very thorough, basic research. In that sense, we oppose special earmarking of a certain amount of money in this deserving category because we feel that our own interest in the disease and the overall strategy we have developed will allow for a broader range of approaches in research. I think it gives the scientists the opportunity to do what they do best, which is to look for the answers to our

medical problems. I think tying their hands by earmarking funds is not the right approach.

Senator GRASSLEY. At this point, I will note that the House Subcommittee on Health and Environment has line-itemed $17 million to the Institute on Aging for research.

Could you also comment on whether there is a lead agency that is currently working on Alzheimer's research?

Secretary HECKLER. Actually, it would be a combination of the institutes on the new task force, and under the direction of Dr. Brandt, who is our Assistant Secretary for Health and chairman of the task force.

Dr. Wyngaarden, perhaps you would like to respond on this?

Dr. WYNGAARDEN. I think that is correct. There are three institutes involved in Alzheimer's research, and a fourth that also participates in such research. The institutes do approach the problem from somewhat different points of view. The National Institute on Aging is understandably interested in Alzheimer's disease because it is a major problem of the aged population; the National Institute of Neurological and Communicative Disorders and Stroke is involved because this is a major neurological disease; and the National Institutes of Mental Health is involved because Alzheimer's disease has important psychiatric and psychological components. The National Institute of Allergy and Infectious Disease supports some relevant activities in this area because there are potentially immunological aspects of this disease that are being investigated. These efforts are very well-coordinated, both within the NIH and within the Public Health Service, through the task force that Secretary Heckler has identified.

Senator GRASSLEY. I now call on Senator Denton for a statement and/or questions.

Senator DENTON. Thank you very much, Mr. Chairman.

I just have a brief comment or two. I want to acknowledge that I believe that the elderly are going to continue to receive the care from Congress which they deserve, from the Senate in particular, now that Senator Grassley has assumed the leadership of a new subcommittee that is separately prescribed to deal with the aging. I think that is a major, important step. Aging was included, as the Senator mentioned, under the jurisdiction of the subcommittee that I chaired during the 97th Congress.

I do want to remind the Secretary that I do have some important aging programs left—Senior Companions Program, Foster Grandparents, RSVP, and so on—and I am extremely interested in them. Through that interest, I have found that the elderly are one of the truly untapped resources in this country today, and that is related to what the National Institute on Aging is saying here about, "Senility: Myth or Madness?" and Alzheimer's disease. In much the same way, emotional problems can be mistakenly confused with irreversible brain disease, depression, loss of self-esteem, loneliness, anxiety, and boredom. These symptoms can become more common as elderly persons face retirement, the deaths of relatives and friends, and other such crises, often at the same time.

These days with the breakdown of the family and the interruption of dependence upon and mixing with the extended family, including the grandmothers and grandfathers, the elderly have a

tendency to become more lonely. In my own mother's case, she had become withered with arthritis at 73; her memory was almost as bad as mine. I put her back to work on a volunteer basis. Eighty percent of her arthritis disappeared; her mind became five times sharper than mine, as it always was. Now, when we are about to celebrate her 80th birthday in a big way, she is 20 years younger than she was at 70, mentally, and even physically.

So to me, it is a real, undiscovered world that we are looking at here, and I hope we do come up with the parameters and cures that will cause a lighter and more minimal effect on our elderly people.

The best fishermen I know are older men in their eighties. I fish every time I get the possible chance, and they are the ones who are wise and alert and know how to get those bass to come out of the water after that surface plug.

I want to commend the chairman for his judgment in choosing this subject as the first subcommittee hearing. Also, it is my understanding that this is the Secretary's first visit to a subcommittee over here, so it does bode well for the pursuit of this particular problem.

I want to commend you all for that, and that is all I have in the way of an opening statement. I do have a couple of questions here, Mr. Chairman.

Senator GRASSLEY. Proceed with your questions.

Senator DENTON. As Alzheimer's disease remains undetected in many elderly patients, are there any statistics that estimate the number of Alzheimer's cases that are diagnosed incorrectly? Is there a qualitative estimate?

Secretary HECKLER. I am afraid that I will have to ask Dr. Mayer for his comment. He perhaps has the figures.

Dr. MAYER. Thank you.

Mr. Chairman, Senator Denton, we estimate that about 15 percent of Alzheimer's disease patients are misdiagnosed. This is partly because the disease can occur concommitantly with small strokes, for example, which can produce similar kinds of symptoms and manifestations. An extensive workup is necessary to be sure of the diagnosis. Even in the presence of that, we think about 15 percent are probably in error.

Senator DENTON. Thank you, sir.

What are the consequences to the victim when the condition remains undiagnosed, and there is no treatment, and what, specifically, are some of the treatments for an Alzheimer's patient—if that is not repetitive of something that the chairman has already asked?

Secretary HECKLER. I again defer to Dr. Mayer.

Dr. MAYER. Sir, there are as yet no specific treatments for Alzheimer's disease. However, in the quality of life that can be provided for such patients, the role of the family is exceedingly important. The quality of care in nursing facilities is equally important. We are hopeful that some of the preliminary research findings with respect to some of the drugs that Secretary Heckler mentioned will lead us, not necessarily through those particular drugs, but lead us to ultimate therapeutic approaches that have a real effect.

Senator DENTON. I have been holding a series of hearings on the breakdown of the family and have looked at the effects on children and the effects on adults in two separate hearings, and usually, the adults were the husband and wife. But I realize that I have got to go back and add another one, and that is the effect on the grandparents. The only aging issue addressed was the desire for visitation rights and that sort of thing, particularly when the situation was rather chaotic concerning the children. That is not enough, because there is an effect on them, and I will have a special hearing on that.

Mrs. Heckler, what is the extent of private sector involvement in advancing research, and are private sector resources significantly offsetting the cost of research at this time? Do you foresee any possibility of increased involvement on the part of the private sector?

Secretary HECKLER. We are very encouraged and grateful to the private sector. They have been very helpful. I mentioned that there are a number of publications which they have helped make possible.

Recently, I visited the Parkinson's Disease Center at the University of Miami, which has been expanded to include clinical services for Alzheimer's disease patients, and met with the researchers and the patients, and I saw, certainly, a wonderful treatment center. I understood and could witness firsthand the degree of the problem and especially the devastation of the family members who in each case were with the patients, and could see by their eyes and their expressions and their private comments to me, how terribly difficult this is for them. I have seen in that case, the private sector which funds the Parkinson's Disease Center, aiding in the funding for the Alzheimer's disease patients. They provide clinical services which are not funded by NIH. Major funding is provided by the Parkinson's Foundation—chaired by Bob Hope, I might add—and the clinical services are provided by the neurology department. The Alzheimer's Association itself is supporting a number of investigations, it gives small grants to young investigators and investigators new to this particular field. So that I think that we are quite impressed with the private sector cooperation in the field, and hopeful that the research, that seems promising at this time, will yield results for what is such a serious disease.

I would like to just say to you, Senator, in terms of discussing the family, you mentioned what I consider to be one of the greatest problems of the elderly today, and that is what I call the "Big L." We are concerned with the "Big C" in terms of cancer, and people are very concerned about that. But among the elderly, I think if society only recognized the "Big L"— the loneliness—of older Americans. If we opened our lives and our minds and our hearts to them in a more personal way, we would deal with the greatest social problem that I think exists among the elderly. I think it is incumbent on all of us in every role to deal with the problem. Of course, in the terms of Alzheimer's disease, we are dealing with a uniquely tragic situation, where there is not merely the issue of isolation, but the issue of a disease. But fortunately, we are funding grants, which I have mentioned earlier, to study the needs of the families, to look at therapy, counseling, and other approaches with them, and to give them support. This will become an increasingly

important need, as our aging population increases. And, if we are fortunate, we will all become elderly. So we see, this is a group in our society that has always been special and will become more so not only because of their relationship to us, but simply because of the demographics of the country. This deserves all the attention that you and Senator Grassley are so wisely devoting to it.

Senator DENTON. The tragedy is double. The elderly may only need the inclusion into what was formerly the traditional family group and now, with the increasing number of divorces and mobility of our society, the children have a special need for contact with their grandparents for their well-being. So there is a double-edged need, not only for the benefit of the elderly, but also for the benefit of the children.

We will have to look at what is the proper Federal role in terms of function and finance, and as is being argued now in the educational field—what is the Federal role, what is the State role. How much of this is Federal, and how much should be done at the State level and at the family level. I certainly see a Federal role. I see a need for research sponsored by the Federal Government into Alzheimer's disease. I just wonder if you are conscious that one of the things we need to look at before we undertake the Federal Government solution to this problem, or undertake searching for it, is to ascertain the proper level or locale, as it were, for the principal handling, or the incremental handling of the efforts to alleviate this disease. You are not looking at this as something that you have already grasped, and that we should completely take care of here in Washington, are you?

Secretary HECKLER. I wish we could, I would feel a lot better if I felt we could find a "Washington answer" to this disease, or a single answer. What we are trying to do at the Department with our task force, is to bring together the research institutes investigating the disease with the programmatic agencies dealing with the concerns and needs of the elderly, such as the financing agency, the Health Care Financing Administration. The goal will be to coordinate the research, to determine the most promising areas of investigation, and to support it. I think that one of the most important things for our HHS research institutes to do—which are a great treasure of the United States in terms of research capability—will be to find through research the medical answers. Then we, as a society, will have to deal with the determination of our other responses, both the response of financing, which will also be on the agenda of the coordinating task force, and the response of society in terms of our own modes of operating, our support systems, and the treatment of these patients. And this is one of the reasons that I wanted this particular task force to include the scientists and those who are in the substantive fields of dealing with elderly programs. In this way we can use any research breakthrough that hopefully we will find and incorporate it into policy changes. But we will always need the private sector, as individuals in this society, to respond with the best information. There is always going to be the private role, so that we will look at all of these factors.

At the moment, we are placing our greatest emphasis on trying to find the medical clues that can unravel the mystery of this dis-

ease. And you will hear some of the researchers I personally have met with a number of the young researchers, and they are very bright and very, very dedicated.

Senator DENTON. Did you say the medical improvements, Madame Secretary?

Secretary HECKLER. Yes, I said the medical answer. We are looking for a medical answer. That is the first priority—I think, to try to reverse the disease if we can, or prevent it, and certainly, improve the diagnosis of the disease. If we find the medical answers, we are going to be able to deal more effectively with the whole disease.

Senator DENTON. But this is not to deny that there may be, in sort of the psychological field, a tremendous——

Secretary HECKLER. Well, no. I include in the term "medical answers", mental health as well as physical health.

Senator DENTON. Yes. Well, thank you very much, Madame Secretary. You obviously have the energy and the imagination to do a great job up there.

Thank you, doctors, and thank you, Mr. Chairman, and again, congratulations for your choice for your first hearing.

Senator GRASSLEY. Thank you, Senator.

I want to say it is refreshing to have a Secretary who is working on a partnership between the private sector and the public sector, and even to admit that the Federal Government may not have a solution to this or may not be the only place to seek one.

I want to suggest that probably a "Heckler" will make a difference in HHS, the same way that a few years ago, you mentioned that the House needed a "Heckler," and a "Heckler" there made a difference, and I am sure a "Heckler" in HHS will make a difference.

I want to thank you for your testimony and your valuable contribution, not only you, but also Dr. Wyngaarden and Dr. Mayer. And let me suggest that, since the other subcommittee members have not been here and may not be able to be here, you may expect some questions in writing from other subcommittee members. The record will be open for any other comments you have, but we would also suggest that if you get those written questions, that you respond, so that we can have them as part of the record, as well.

Thank you very much.

Secretary HECKLER. We would be happy to respond, Mr. Chairman, And I can tell you, I always intend to continue to be a "Heckler," on Alzheimer's disease as well.

[Information supplied for the record follows:]

National Institute on Aging

Age Page

Senility: Myth or Madness?

"Senility"--something which most of us fear in old age--is not a normal sign of growing old; in fact, it is not even a disease.

Rather, "senility" is the word commonly used to describe a large number of conditions with an equally large number of causes, many of which respond to prompt treatment.

The symptoms of what is popularly called "senility" include serious forgetfulness, confusion, and certain other changes in personality and behavior. While doctors and patients alike used to routinely dismiss these symptoms as incurable effects of old age, they are not necessarily. Nor are small memory lapses in old age a sign of "senility." Slight confusion or occasional forgetfulness throughout life may only signify an overload of facts in the brain's storehouse of information.

Mental decline in old age might be called "dementia," "organic brain disorder," "chronic brain syndrome," "arteriosclerosis," "cerebral atrophy," or "pseudodementia." The important thing to remember is that some of the problems which are generally referred to under the medical description of senile dementia can be treated and cured, while others, at this time, can only be treated without hope of restoring lost brain function. Thus a complete, careful investigation of the source of the symptoms is necessary.

Diagnosis

The two most common incurable forms of mental impairment in old age are multi-infarct dementia and Alzheimer's disease (pronounced altz'hi-merz). Multi-infarct dementia is caused by a series of minor strokes which result in widespread death of brain tissue. This condition accounts for about 20 percent of the irreversible cases of mental impairment. In Alzheimer's disease changes in the nerve cells of the outer layer of the brain result in the death of a large number of cells. Some 50 to 60 percent of all elderly persons with mental impairment have Alzheimer's disease.

Some 100 reversible conditions may mimic these disorders. A minor head injury, a high fever, poor nutrition, or adverse drug reactions, for example, can temporarily upset the normal activity of extremely sensitive brain cells. If left untreated, such medical emergencies can result in permanent damage to the brain, and possibly even death.

In much the same way, emotional problems can be mistakenly confused with irreversible brain disease. Depression, loss of self-esteem, loneliness, anxiety, and boredom can become more common as elderly persons face retirement, the deaths of relatives and friends, and other such crises--often at the same time.

Persons suspected of having Alzheimer's disease or multi-infarct dementia should have thorough physical, neurological, and psychiatric evaluations. This includes a complete medical exam, as well as tests of the patient's mental state, and highly specific tests such as the brain scan. The brain scan is useful in that it can rule out a curable disorder. The brain scan may also show signs of normal age-related changes in the brain, such as

(over, please)

shrinkage, which are not necessarily a sign of disease.

The patient plays an important role in the diagnosis by giving information on past medical history, the use of drugs--both prescription and over-the-counter--diet, and general health. Because part of the medical exam depends upon how much a patient is able to remember about past events, the doctor may also ask a close relative for information.

Treatment

The best treatment comes only after a complete medical examination by one who does not dismiss complaints as "just old age." If there is a diagnosis of a curable disease, the doctor will know how to treat it or will have ready access to the best resources or specialists.

If the diagnosis is one of the irreversible disorders, there is still much that can be done to treat the patient and to help the family cope. Careful use of drugs can lessen agitation, anxiety, and depression, and improve sleeping patterns if this is needed. Proper nutrition is particularly important, although special diets or supplements are usually not necessary. The person should be encouraged to maintain daily routines, physical activities, and social contacts, and should not be discouraged from trying new things. Often, stimulating the individual--by supplying information on the time of day, place of residence, and what is going on in the immediate environment and in world events--encourages the use of skills and information which remain. This in turn may keep brain activity from failing at a more rapid pace. In the same way, providing memory aids helps people help themselves in day-to-day living. Such aids can include a very visible calendar; list of daily activities; written notes about simple safety measures; and directions to, and labeling of, commonly used items.

In any event, a patient with an irreversible disorder should be under the care of a physician. This may be a neurologist, psychiatrist, or family physician or internist--who is willing to devote the time and interest required to closely watch treatment; to treat the physical and emotional problems that may complicate the course of the disease; and, of course, to answer the many questions that the patient and family may ask.

There are many differences in the type, seriousness, and order of changes in cases of irreversible dementia. Even so, there is enough similarity in the experiences of patients and their families--the loneliness, the frustrations, the lack of information and resources for good medical care--to have led to the development of family groups around the country. Recently, seven such groups formed the Alzheimer's Disease and Related Disorders Association (32 Broadway, New York, NY 10004) to encourage research, education, and family services.

Prevention

Diet, drugs, and lifestyle may someday be used to prevent or reverse the damage done to the brain in Alzheimer's disease and other related diseases. At the present time, however, our understanding of these problems and their causes is just beginning to unfold.

Developing interests or hobbies and becoming involved in activities which keep the mind and body active are among the best ways that the elderly can avoid the problems which can mimic irreversible brain disorders. Careful attention to physical fitness, including a balanced diet, may also go a long way towards keeping healthy. There appear to be certain physical and mental changes which occur with age even in healthy persons, but in the long run, much pain and suffering can be avoided if the elderly, their families, and their physicians realize that "senility" is not part of aging.

October 1980

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service National Institutes of Health

Senator GRASSLEY. We have a very distinguished panel of witnesses who are now going to testify: Dr. Murray Goldstein is the Director of the National Institute of Neurological and Communicative Disorders and Stroke. Dr. Herbert Pardes is the Director of the National Institute of Mental Health, and Dr. Robert Ringler is the Acting Director of the National Institute on Aging.

Gentlemen, we are very interested to hear what you have to tell us on this very important subject with which we are wrestling for information and direction.

Dr. Goldstein will proceed and then please follow in the order in which we call upon each of you. I know that each of you has had plenty of experience testifying before committees, and you know the practice of placing the entire statement that you have in the record, and beyond that point, summarizing, if you could, because we have some questions that we want to ask as well.

So, would you like to proceed, Dr. Goldstein?

STATEMENTS OF A DR. MURRAY GOLDSTEIN, DIRECTOR, NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE; DR. HERBERT PARDES, DIRECTOR, NATIONAL INSTITUTE OF MENTAL HEALTH, AND DR. ROBERT L. RINGLER, ACTING DIRECTOR, NATIONAL INSTITUTE ON AGING, A PANEL

Dr. GOLDSTEIN. Thank you, Mr. Chairman.

I trust my prepared statement describes the research activities of the NINCDS. For the sake of brevity, I will call it the Neurology Institute from here on. My oral statement will summarize some of the major points in that written statement.

The Neurology Institute is the focal point at the NIH for the conduct and support of research on the neurological disorders of the brain and spinal cord, and also, most importantly, those uniquely human characteristics of speech and language. This includes research on Alzheimer's disease and the other neurological disorders which share the common feature of dementia, such as Parkinson's disease and Huntington's disease.

As the Secretary has pointed out, we now define Alzheimer's disease as a dementia due to specific pathological changes in the brain, irrespective of the age of the patient. Previously, this disease was thought to occur only in persons between the ages of 40 and 60, and what was then called senile dementia would be another disease. It now turns out that these are the same disease.

The outstanding characteristic of the Alzheimer patient is loss of memory. It is important to differentiate loss of memory from forgetfulness. For example, I am approaching that stage where, every now and then, I forget where my glasses are. The Alzheimer patient does not forget where he or she placed a pair of glasses; they forget that they wear glasses—a complete erasure of that information from the memory storage bank.

The issue we face in research on neurological diseases is how to find out what is happening within this organ called the brain, what is afflicting this patient. Unfortunately, at the present time, the definitive diagnosis of Alzheimer's disease can only be made under

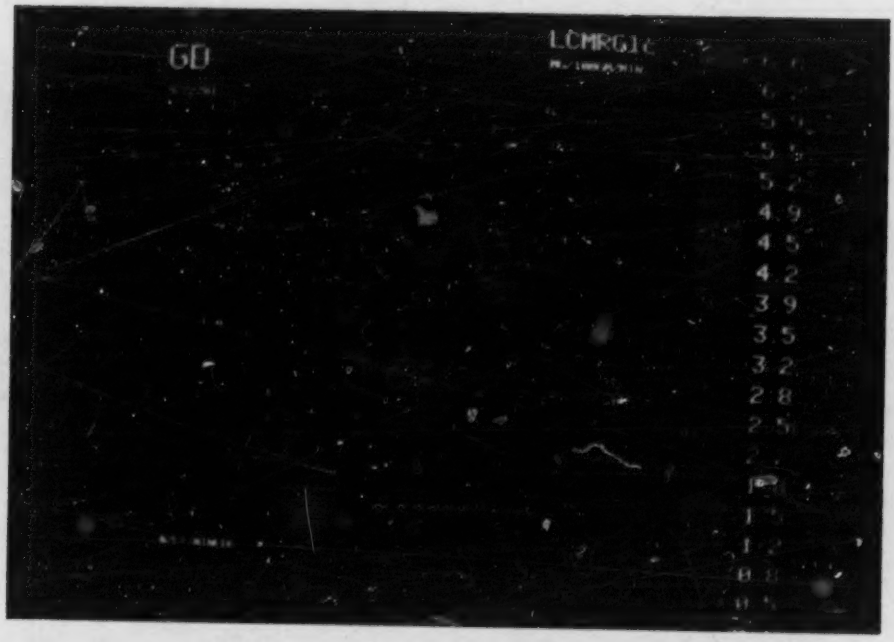
the microscope. However, we are developing new methodologies which permit us to look inside the brain, the living human brain, and that is called positron emission tomography (PET).

Mr. Chairman, for your interest, I have a color photo here which you might find of value. This is a PET scan of the brain of a patient with Alzheimer's disease. This looks inside the brain of a living woman, age 65. She has lost what we call spatial concept. Because of a lesion on the right side of her brain, she has forgotten how to dress herself; she sometimes puts her clothes on upside-down. If she wanders into a closet, thinking it is the living room, she becomes frozen in it—does not remember that it is a closet, does not remember how to get out. She cannot set the table. She does not know where the knives and forks go.

Previously, we thought this was a mishap affecting the entire mantle of the brain. What the picture of her brain shows you is—and it is the area which is black, around the orange area—that there is a focal lesion. That is the specific area of the brain which is not working. The orange demonstrates that part of the brain which is burning glucose for energy. That energy ought to be produced all over the brain, but in this particular patient with Alzheimer's disease, we find that a specific area of the brain—specific area, I continue to emphasize—is not functioning properly.

Senator GRASSLEY. Would you point to it in the picture, please?

[The information referred to follows:]



PET scan of the brain of a 65-year old woman suffering from Alzheimer's disease. The bright areas represent parts of the brain where nerve cells are still actively burning glucose. The dark areas in the lower right side tell us that cells are no longer functioning in this area of the brain which governs spatial concepts. In this woman, the loss was manifested by inability to put her clothes on correctly or to set the table properly.

Dr. GOLDSTEIN [indicating].

Senator GRASSLEY. Thank you.

Dr. GOLDSTEIN. The orange colored mantle of cells indicates burning of energy in all the areas of the brain, and, as you remember, sir, the brain generally uses only sugar for its energy. So we can "label" that sugar and watch it being used inside the human brain without opening the head. This is a harmless procedure.

Senator GRASSLEY. Now, at this point, that damage would be permanent in that there would be no way for that to regenerate?

Dr. GOLDSTEIN. I do not know, sir. I hope the statement you have made is accurate.

Senator GRASSLEY. At least, elaborate on what you know now.

Dr. GOLDSTEIN. At the moment, we know of no way of restoring the function which has been lost. Now, the issue is why is this occurring, and what is happening inside that brain that causes this metabolic lesion. We do know that the brain requires very specific kinds of neurotransmitters to function. A neurotransmitter is a chemical which one nerve cell produces to send information to the next cell. That is how information is transferred through the cells of the brain and the entire nervous system.

One of the most important of these neurotransmitters chemicals is acetylcholine. That chemical is produced in one cell and sent to the other cells with a message. We know that in the brain of the Alzheimer patient, there is a tremendous loss of acetylcholine; this chemical is just not there. Therefore, we are not surprised that cells that require information from other cells which use acetylcholine are not being adequately informed without this neurotransmitter.

Now, the question is: Why is this neurotransmitter not present? I will not bore you, sir, with the chemistry of neurotransmitters. But the key point that we have learned, and to reinforce the statement the Secretary made, it has been learned by collaborative research supported by the three Institutes represented at this table, is that there is a specific area underneath the mantle of the brain, a very small nucleus, which we have now learned no longer functions in the Alzheimer patient. And so, what we are discussing in Alzheimer's disease is a disorder of the mantle of the brain, affecting specific areas that require another area of the brain, which we now know is not functioning in the Alzheimer patient and which stimulates and activates the mantle of the brain.

Now the interesting question, of course, is why that happens. We do not yet know the answer to that. There are many theories, and my written statement presents some of those to you. But I would like to emphasize one issue which may be one of the most important areas of research for the future. That is the programed death of cells. We have learned about infection. We have learned about immunological reaction. We have learned about a lack of blood supply to specific areas of the brain causing a stroke. But we are now approaching an era where we are beginning to understand that somehow or other, built into our genetic system—and I am not calling Alzheimer's disease a genetic disease—but built into our human genes, certain cells of the brain turn off at a preprogramed time and stop working. The most outstanding example of this is a terrible disease of younger people, middle-aged people, called Hunt-

ington's disease, a true genetic disorder, where a vital part of the brain, producing important chemicals, stops working for a genetic reason. This raises the whole issue of the preprogramed "turn off" of cells of the brain. It is this exciting area of research which the three Institutes are also pursuing in an attempt to get an understanding of what it is we are dealing with.

And so, Mr. Chairman, through positron emission tomography, we are now able to watch the human brain at work, without harm to the patient. Through immunological and vascular studies, we are beginning to understand how the brain reacts to its environment. And through biochemical and genetic studies, we are hoping to understand this programing of why things get turned on and why things get turned off as the human organism develops and ages.

In summary, sir, I can say this. Alzheimer's disease is a disease of the brain. It is not a normal consequence of the aging process. Let me repeat: It is not a normal consequence of aging. It is a disease, and being a disease, it should be treatable, and, we hope, preventable. The Neurology Institute of NIH looks forward to participating in the Interagency Task Force, and we would hope to be able to pursue research leads until we can eventually eradicate Alzheimer's disease as a disorder of our aging population.

Thank you, Senator.

Senator GRASSLEY. Thank you, Dr. Goldstein.

[The prepared statement of Dr. Goldstein follows:]

ALZHEIMER'S DISEASE - TESTIMONY

Dr. Murray Goldstein, Director
National Institute of Neurological and Communicative Disorders and Stroke

Mr. Chairman, I am the Director of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) of the National Institutes of Health (NIH). The NINCDS conducts and supports research on the neurological disorders of the brain and spinal cord and those uniquely human characteristics of speech and language. This includes research on Alzheimer's disease and on other disorders of the brain which share clinical features of dementia, such as Parkinson's disease and Huntington's disease. I am here today to summarize for you examples of that research, specifically, what neurological research has taught us about Alzheimer's disease. I am going to discuss the signs and symptoms of Alzheimer's disease as well as the several different hypotheses of its causes. Finally I will provide examples of ongoing neurological research on Alzheimer's disease.

Diagnosing the Alzheimer's Disease Patient

Before I summarize what is known about the basic disease process, I want to clarify that I am using the term Alzheimer's disease to include all dementias of the Alzheimer's type, regardless of the age of the patient. I am discussing a dementia that is due to specific pathological changes in the brain. Thus, I include both those persons in their 40's, 50's and early 60's who have what was called Alzheimer's disease in the past, as well as those older Americans with dementias of the Alzheimer's type. I wish to differentiate these patients with Alzheimer's disease from those

with depression or drug-induced problems and from those with multi-infarct dementia caused by "hardening of the brain arteries" or by multiple small strokes.

The Alzheimer's disease patient comes to the physician because of changes in mental abilities, personality and behavior or may exhibit marked confusion, disorientation and memory loss. The forgetfulness of Alzheimer's disease is far different than the transitory forgetfulness or absent-mindedness experienced at any age. Unlike the benign forgetfulness of not remembering where you put your glasses, the malignant forgetfulness of Alzheimer's disease means that the patient forgets that he or she wears glasses at all. While benign forgetfulness is general and sporadic, the forgetfulness of Alzheimer's disease is very specific. Patients no longer remember how to dress properly, for example, how to tie their shoelaces or close a zipper, and keep making the same mistake each time they dress. The patient may show signs of hostility or evasiveness even to loved ones who are the closest family members.

When confronted with a patient whose dementia may be due to Alzheimer's disease, physicians conduct a range of neurological tests to determine if the patient's confusion and other symptoms have a neurological basis in the organic structure and function of the brain. Patients with Alzheimer's disease will demonstrate this organic basis to their disease. The patient's reflexes will be examined, as will his or her stance or walk. Like Parkinson's disease, Alzheimer's disease has particular movement signatures. Many Alzheimer's disease patients have a slow gait, with drooped posture. Often, arm swing is almost absent and they take mincing steps from a wide-based, flexed stance.

To test the patient's higher functions, the physician will use an oral test, called the Mental Status Questionnaire (MSQ). This test is comprised of 10 simple questions, such as "Where are we now?" "What is today's date?" "What month is it?" "How old are you?" "When is your birthday?" "Who is the President of the United States?" and, "Who was the President before him?" While patients in the early stages of Alzheimer's disease may score reasonably well on this test, many Alzheimer's disease patients will rate as severely or moderately confused.

The patient's ability to travel alone on public transportation, to get dressed without help, and to bathe without assistance are also considered as is the ability to shop, cook, or do ordinary household tasks alone. Tests of this sort specify the patient's level of impairment.

At the first visit to the physician, definitive diagnosis can be difficult. Other neurological or psychiatric disorders can present with features that resemble the signs and symptoms of Alzheimer's disease. A major characteristic of Alzheimer's disease is its downhill progression. Physicians suspecting the disease in a patient will repeat the initial round of tests at six-month intervals. If the patient has worsened, Alzheimer's disease may well be the diagnosis.

Basic Theories of Alzheimer's Disease

At this time the definite diagnosis of Alzheimer's disease can only be made under the microscope, usually at autopsy. The brain of the

Alzheimer's disease patient has several unique characteristics. It has specific anatomical lesions called neurofibrillary tangles and neuritic plaques. Neurofibrillary tangles are made up of fine nerve filaments twisted around each other. They are found in the cell bodies of the brain cells. Research has disclosed that the tangles are made up of an abnormal protein that is particularly insoluble and hard. The implication of the insolubility of the tangles is unclear. Yet, we are confident that the tangles should not be in the brain and are probably there permanently.

The neuritic plaques are also composed of an abnormal protein. We believe them to be degenerating bits of the nerve cell endings that surround a core of fibrous protein material. They are sometimes called the senile plaque. The protein in the core is similar to the protein which makes up antibodies. I have elaborated on the plaques and tangles in the brain because they are crucial to our ideas of the cause of Alzheimer's disease. We do not yet understand them, but we have observed that they are associated with the severity of the patient's disease: the more plaques and tangles there are, the more severe the patient's symptoms. The number of tangles and plaques is an indicator of the progression of this organic disease of the brain.

In the mid 1970's three independent groups of scientists, all working in the British Isles, discovered that a particular enzyme, choline acetyltransferase--CAT for short, was practically gone in the brains of patients dying with Alzheimer's disease. CAT is involved in the process by which a key neurotransmitter, acetylcholine, is made in the brain cell.

Other scientists had demonstrated earlier that acetylcholine was the chemical used by nerve cells to communicate with each other and is probably involved in memory.

We have recently learned the probable location in the brain of the changes that are involved in the memory loss and general deterioration of Alzheimer's disease. Scientists at The Johns Hopkins University discovered that cells deep in an area underlying the mantle of the brain, the basal forebrain, are the site of the lesions I've described. The nerve cells in this part of the brain send fibers to many parts of the mantle of the brain and to a specialized area of the brain important to memory called the hippocampus. These nerve cells use acetylcholine as their neurotransmitter. In Alzheimer's disease patients, the Johns Hopkins' scientists discovered, the basal forebrain neurons had degenerated. We believe that the death of these cells may cause the brain damage of Alzheimer's disease, leading to the clinical symptoms of intellectual loss. Thus we can now tie together the loss of the enzyme CAT with the specific location of the neurons which die in Alzheimer's disease.

We do not yet know why these neurons die or what causes the neurofibrillary tangles and neuritic plaques. There are several hypotheses offered to explain the situation--specifically, to explain what causes Alzheimer's disease. In one approach, scientists are testing the idea that the body mounts a self destructive attack as a response to the abnormal proteins seen in the tangle and the plaque. On the other hand, we must recognize that the tangles and the plaques may be the result of the brain's attempt to protect itself against some as yet unknown invader.

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The blood-vessel theory is another possible reason for the disease. The blood-brain barrier is a cellular wall that protects the brains of healthy people from materials that could enter the brain from the blood stream; viruses, bacteria, and other substances that could possibly harm the brain. According to this theory, the blood-brain barrier is violated and the culprit enters the brain substance and damages it in such a way as to cause Alzheimer's disease.

The immunological and blood-vessel theories provide alternative explanations of how the brain is devastated. But what affects the brain? What activates the immune system or passes through the blood-brain barrier? Scientists have several different theories. One is the genetic theory. Although Alzheimer's disease doesn't follow strict Mendelian laws of inheritance, the disease sometimes occurs in families. While the average person's chance of developing the disease is about 1 percent, the odds increase four-fold or more if a close relative is affected. There is no clear-cut genetic component but we suspect a genetic aspect, perhaps a genetic predisposition or propensity to the disease. We need to study further those families in which there are clusters of victims.

A second theory of the causation of the disease is the viral theory. Scientists have noted that patients with kuru, another dementing disease, have similar brain plaques. Kuru is a viral disease of the brain caused by one of a class of agents known as slow viruses. These organisms incubate in the nervous system for decades before becoming active and causing damage. Investigators have also seen similar plaques when they inoculate

mice and hamsters with scrapie, another slow virus that ordinarily affects sheep. Important in its own right for its significant damage to sheep, scrapie provides a potentially valuable animal model and allows us to investigate this viral theory.

The environmental theory offers still another explanation. Aluminum, the third most common element, is found in higher than usual concentrations in the brains of Alzheimer's disease patients. Aluminum has been found in the neurofibrillary tangles by scientists in our Intramural Research Program at Bethesda. Aluminum, as we know, is toxic to the brain and causes abnormal brain function. Research on the role of aluminum and other minerals is continuing.

Research Leads

The PHS is currently conducting a full slate of research on Alzheimer's disease. The Positron Emission Tomography (PET) Program is evaluating human brain metabolism in various disease states, including Alzheimer's disease. The basic research the PHS supports and conducts should uncover clues into the cause, treatment, and eventually prevention of Alzheimer's disease. Research on the organization of the brain and its neurotransmitters will uncover new information that promises to lead to a better understanding of the brain, the way we think, and how our memory works. Eventually this work will help us understand Alzheimer's disease.

Specific research is also targeted on the disease process. Time does not allow me to catalog that work in detail, but a few examples may be useful. Scientists funded by the Public Health Service are studying a putative new agent, the prion, to determine if Alzheimer's disease has an infectious origin or component. Scientists, also supported by PHS funds, are using immunological techniques to study the origin of neurofibrillary tangles and other facets of the disease. Investigators are studying the unusual properties of the tangle proteins which make them so resistant to solution, and one group of scientists is tracing the specific connections of the nerve pathways involved in higher mental functions. Hormones and neurotransmitter relationships in the brain are being studied by scientists with Public Health Service support.

Applied research is also underway. Positron emission tomography (PET) scans of Alzheimer's patients have allowed us to correlate specific metabolic changes in the brain with specific symptoms in Alzheimer's disease. We can see that energy utilization is greatly reduced in a specific part of the brain associated with the ability to solve simple puzzles in those patients who have lost that particular skill. In patients whose ability to use the appropriate words in conversation is impaired, the areas of the brain involved in speech have greatly decreased function. The Public Health Service is funding scientists who are trying to devise more accurate tests for early diagnosis of Alzheimer's disease. These investigators are conducting a longitudinal study of an aging population and hope to increase our understanding of the natural history of Alzheimer's disease and other progressive dementias. From studies like this, we should get better ideas of risk factors for the disease.

In summary, we now can say with certainty that Alzheimer's disease is a disease of the brain--it is not a normal consequence of the aging process. It is a disease--and therefore, should be preventable and treatable. Scientists on the NIH and ADAMHA intramural campus and in laboratories around the country are working towards this objective. The NINCDS looks forward to participating in the newly formed Departmental Task Force, which I am certain will be most helpful in coordinating these scientific efforts and bringing their results rapidly into clinical practice.

Thank you for the opportunity of describing these exciting scientific advances being made about this devastating disease. I would be pleased to answer any questions the Subcommittee may have.

Senator GRASSLEY. Dr. Pardes?

Dr. PARDES. Thank you, Mr. Chairman.

I am pleased to testify before the Subcommittee on Aging of the Committee on Labor and Human Resources, regarding the National Institute of Mental Health's (NIMH) commitment to the advancement of our understanding and treatment of Alzheimer's disease.

When the specter of this illness stands before us all as we age, it is heartening to know that national attention is being focused on the problem. To have such distinguished Senators as yourself and the members of this subcommittee join forces to halt this devastating disease is immensely gratifying.

We once thought that senility was the price for old age, as Dr. Goldstein stated. If you lived long enough, eventually, you would lose the clarity of your mind. Now we know that a dread disease robs us of our mental faculties, as stealthily and silently as any thief.

Our new knowledge of Alzheimer's disease as an illness is very hopeful, because it means that it may be amenable to well-developed research strategies. But we have a long way to go to achieve understanding of this severe disorder, and we certainly do not know which one of us is susceptible to attack.

I am proud of the role NIMH is playing in stimulating and supporting scientific and public activities related to Alzheimer's disease. We are exquisitely aware, Mr. Chairman, of the enormous personal and social disruptions caused by this terrifying disease. At the same time, we are encouraged by recent scientific information which suggests that this disorder does not have to be perceived with the stark and utter pessimism that heretofore has characterized it.

Much remains unknown but the support for scientific evidence has begun to prove fruitful. The NIMH investment in research on

aging has increased sixfold in the past 7 years. When combined with our major commitment to the neurosciences, the effort represents a considerable portion of our budget. Currently, our research effort specifically directed to Alzheimer's disease is $5 million. Seventy percent of this is clinical, behavioral and psychosocial. About 30 percent is basic research.

In addition, NIMH spends $19 million for research in the neurosciences, 60 percent of which is basic science, 40 percent, clinical. Mr. Chairman, my written testimony contains detailed information about NIMH efforts, both alone and in collaboration with my Institute Director colleagues and their Institutes.

In my few minutes, I would like to highlight certain NIMH activities which indicate the directions in which our programs are moving. There are recent developments both in mental health research generally, as well as in research focused on Alzheimer's disease, which deserve comment.

A recent breakthrough is the 2-deoxy-D-glucose method, which is used in conjunction with the positron emission tomography, or PET scanner, that Dr. Goldstein referred to a moment ago. This is used to look at how the living brain functions. For developing this method, Dr. Louis Sokoloff of the National Institute of Mental Health received the Lasker Award. The PET scanner, a noninvasive brain-imaging technique, is a dramatic advance enabling us to study systematically activity in the brain. Within both the Public Health Service and at universities such as New York University, UCLA, the University of Chicago, and others, this technique is now being used to investigate neurological and psychiatric disorders, including Alzheimer's disease, schizophrenia, manic depressive disease, and many others. As Dr. Goldstein noted, brains of Alzheimer's disease patients are found to be metabolically less active, less energetic than normal brains.

Progress is also being made in our understanding of the plasticity of brain tissue. By that, I mean the brain tissue's capacity for growth, for change, and especially for repair, as you were asking just a moment ago, Senator.

One of our grantees, Dr. Roger Sperry, discovered that the left and right sides of the brain have different functions. This revelation was recognized in last year's Nobel Prize for Medicine to Dr. Sperry. We are even delving into the molecules which make up genes to uncover the possible genetic contributions to Alzheimer's disease and other neuropsychiatric disorders, as well as to normal behavior. The so-called cholinergic hypothesis of Alzheimer's disease has proved encouraging. In the brains of these patients, the deficiency of acetylcholine, one of the chemical messengers that allows information to travel between neurons, has been reported by researchers at Albert Einstein Medical College. Scientists at Johns Hopkins University have located an anatomical site in the brain significantly involved in the production of acetylcholine, a site called the basal nucleus. These cells seem to be selectively destroyed in patients with Alzheimer's disease.

A second area of productive work is focused on kinds of memory functions impaired in patients with Alzheimer's disease. Investigators in the NIMH intramural program have demonstrated that there are particular memory deficits associated with disturbed

neurobiological functions. When you compare groups of Alzheimer's patients with those of other disorders, Alzheimer's patients seem to have an inability to gain access to information which was previously stored, and this seems to obstruct their capacity to process new information. It is almost as if they do not have a framework on which to put new information. Our scientists are working to clarify further the relationship between this kind of memory disturbance and Alzheimer's disease. While we cannot make any certain statement about diagnosis in any one patient at this time, we are encouraged by our capacity to differentiate kinds of memory disturbances. This will help us in further scientific investigation of the disorder, and possibly, ultimately, also in differential diagnosis.

Yet another research area which came up a little earlier in the testimony, offering some glimmer of hope, is therapeutics. There have been very early findings—I want to stress the preliminary nature of these findings—with some drugs, suggesting potential alteration of symptomatology in Alzheimer's disease. The primary point, however, is that the disorder may be modifiable. While the drugs that might ultimately be most effective in doing that are not known at this time, we are encouraged by these kinds of developments to push further.

A crucial aspect of this disorder, while we work toward an effective treatment and an understanding of its cause, is the plight of present-day sufferers which include not only the patient, but also the family, as Senator Denton was emphasizing. The significant contribution of the family to the Alzheimer's patient has been systematically documented, in NIMH-supported studies at the Philadelphia Geriatric Center, and at the Benjamin Rose Institute in Cleveland. These studies have detailed the severe stress and the enormous burden that accompany such care. Family members of Alzheimer's disease patients, when studied by NIMH grantees at the University of Washington and at the Texas Research Institute of Mental Sciences in Houston, manifest a variety of disturbances including serious clinical depression. Studies at the University of Southern California are exploring interventions to prevent these onerous consequences for the family.

The NIMH is also working to develop adequate numbers of scientists and academic leaders, both to investigate Alzheimer's disease and related issues and also to increase the education of students in the health professions about this disorder.

Further, we are concerned that high-quality information be made available to professional and public audiences as quickly and as effectively as possible, and Mrs. Heckler documented some of our attempts to get the private sector to work collaboratively with us in this effort. Future publications in this series include works on sleep disorders, assessment, and a research-oriented book on experimental treatments for senile dementia and Alzheimer's disease. Again, we are working with the private sector in these efforts.

Our public information sheet on Alzheimer's disease has been distributed and reproduced widely across the Nation, and I have copies here for the record.

I would also like to mention the collegial and collaborative relationships we have had with other agencies and institutes of govern-

ment. NIMH is a member of the Ad Hoc Interagency Committee on Research in Aging, coordinated by the National Institute on Aging. Our joint projects in Alzheimer's disease sponsored by the National Institute of Aging and the National Institute of Neurological and Communicative Disorders and Stroke and NIMH started with a pair of conferences in 1977 and 1978 for which NINCDS and NIMH took the lead on one and the other, respectively.

Currently, research grant applications can be and are assigned jointly to as many institutes as is appropriate, so that each may consider the project for funding. Finally, I am pleased that the NIMH has been given the Executive Secretary function for the Secretary's new Task Force on Alzheimer's Disease. Dr. Gene Cohen, Chief of the NIMH Center for Studies of Mental Health of the Aging and his staff are assuming this function.

Mr. Chairman, I thank you for the opportunity to testify on mental health efforts in the area of Alzheimer's disease, and I would be pleased to answer any questions that you and members of your subcommittee may have.

[The prepared statement of Dr. Pardes follows:]

TESTIMONY OF

HERBERT PARDES, M.D.
DIRECTOR, NATIONAL INSTITUTE OF MENTAL HEALTH
ALCOHOL, DRUG ABUSE, AND MENTAL HEALTH ADMINISTRATION

I appreciate the opportunity to testify before the Subcommittee on Aging of the Committee on Labor and Human Resources on the National Institute of Mental Health (NIMH) basic and clinical research efforts in Alzheimer's Disease. At NIMH we carry out research in our own intramural laboratories and support the research of investigators in the field through grants and contracts. Other activities at NIMH involve support for the education of researchers and clinicians, the development of statistical and informational materials, and national leadership in consultation with both public and private mental health service providers.

The focus for NIMH activities in the area of Alzheimer's Disease is the Center for Studies of the Mental Health of the Aging, one of eleven operating units of the Institute. The Center, made fully operational in 1976, has established Alzheimer's Disease as a major program priority. In 1976 the Center, in collaboration with the National Institute on Aging and the National Institute of Neurological and Communicative Disorders and Stroke, developed two research conferences on Alzheimer's Disease; proceedings of both have been published and are now considered standard resources in the field.

These conferences were the beginning of the focus on Alzheimer's Disease and also laid the framework for a series of collaborative efforts between the Institutes. Such collaborative efforts have involved the joint support of research grants and contracts, joint support of components of research programs at universities and medical centers, and the inclusion of cognitive and behavioral assessments in prevention-oriented clinical trials. Under Interagency Agreements the NIMH has also developed other joint program activities with the Administration on Aging, the National Heart, Lung, and Blood Institute, and the National Institute of Handicapped Research of the Department of Education.

The NIMH research in Alzheimer's Disease is, by design, multidisciplinary in the broadest sense. Investigators from neurochemistry to social work and from

behavioral genetics to health care economics have joined with basic, clinical, and applied researchers in the range of biomedical, behavioral, and social disciplines that are involved in mental health research. Exciting new findings are being reported and creative investigations are being pursued. This report conveys some of the excitement of research in this area.

With the increases in the absolute number and relative proportion of older persons in the general population, growing attention has been focused by NIMH on the devastating and disabling effects of those brain disorders which are associated with advancing chronological age. Among these disorders, Alzheimer's Disease has been estimated to affect more elderly persons than any other brain disease. Because of the decrease in life expectancy accompanying this illness, Alzheimer's disease is thought to be the fourth greatest cause of death in those over age 65 in the United States and other developed nations. As a cause of suffering and death, it is comparable in magnitude to such major illnesses as cancer and heart disease.

Until recently, this major disease was largely neglected by both laymen and physicians alike, and usually not distinguished from aging in general. However, in recent years, both physicians and laymen have shown increased interest in this disorder. In the past decade a considerable amount of progress has been made in the understanding of Alzheimer's disease by scientists around the world. Recent advances have radically altered our thinking about Alzheimer's Disease; whereas in the past, it was considered a normal consequence of aging, it is now known to be a disease entity.

In view of the great need for more fundamental information about Alzheimer's and the dementing disorders of middle and late life, we have actively embarked on a program of support to stimulate researchers to study the problems. The Institute currently supports a wide-ranging of multidisciplinary set of

studies which have both theoretical and applied implications: these include studies of the epidemiology, etiology, diagnosis, natural history, management, and treatment of Alzheimer's and related brain disorders. The Institute's interests range from support of studies applying advances in positron emission tomography (PET) and problems in differential diagnosis, to systematic investigations of the role of the family in sustaining the psychological integrity of the patient with Alzheimer's who is living in the community.

This brief and selective review of current projects in Alzheimer's Disease underscores the recent dramatic advances in research knowledge regarding this dreaded illness, while highlighting the broad commitment to the full range of affective, social, psychological, biochemical, and anatomical concomitants of this serious form of brain pathology in the elderly. In a systematically devised, step-wise approach to the development of research understanding, the Institute has stimulated and supported projects focused on: (1) determining the distribution of Alzheimer's Disease in the general population; (2) determining the causes of the disease, and the nature of its clinical course; (3) formulating more reliable methods of identifying and diagnosing Alzheimer's Disease; (4) developing effective strategies for treatment and management; and (5) evaluating the impact of Alzheimer's Disease on its victims, their caregivers and family, and the health care system at large.

I. What is the Distribution of Alzheimer's Disease in the Population?

Questions from Epidemiological Research

In an effort to examine the distribution of late-life dementias, stratified random samples of the population at major sites across the country are being studied to assess the level of cognitive functions of elderly individuals living

both in the community and in institutions, using rigorous structured interviews, diagnostic instruments, and diagnostic research criteria. Disproportionately large samples of elderly persons have been examined at the Duke University and Yale University sites, and even more intensive psychiatric and neurologic studies are being carried out on the oversample of elderly studied at the Johns Hopkins site in Baltimore. Intensive examinations of brain structure, neurochemistry, and neuropsychology have been carried out on all individuals identified as positive for dementia at the Baltimore site by Drs. Marshall Folstein and Allan Ramanofsky, in addition to complete physical examinations. These major, carefully planned, systematic epdemiologic studies of randomly selected elderly should provide data of inestimable value to investigators around the world. Epidemologic studies of this nature are urgently needed to define the prevalence, incidence, and risk factors associated with this disorder, since available estimates are based on a patchwork of non-comparable studies. Furthermore, most of the currently available information regarding structural, neurochemical, and behavioral differences in the brain functions of Alzheimer patients are based on non-randomly selected samples whose generalizability may be suspect.

II. What Causes Alzheimer's

New hypotheses in research of the elusive cause of Alzheimer's Disease are being vigorously tested in a growing number of studies. These studies focus on etiological factors as diverse as chemical deficiencies, brain lesions, autoimmune disorders, and genetic abnormalities.

Over the last decade, as a result of intramural and extramural research, our understanding of the complex processes involved in brain function

has advanced tremendously. A major area of progress concerns an enhanced understanding of the mechanisms that neurons use to communicate with each other. Neurons have been shown to release chemical messengers, known as neurotransmitters; the specific effects of these messengers are interpreted by receptors on the adjacent neurons. Because the process of chemical neurotransmission can be manipulated by drugs, it represents an important site for the treatment of symptoms resulting from disorders of the brain. A number of drugs are successfully used in psychiatry to treat disorders that involve abnormalities of chemical neurotransmission; these include neuroleptics in schizophrenia and tricyclics in severe depression, to mention a few.

Over the last several years, a number of investigators with support from the Public Health Service (PHS) have examined the brains of patients who have died with senile dementia for abnormalities in chemical neurotransmission. Out of that work, two lines of investigation have provided compelling evidence of impaired function of neurons that utilize the neurotransmitter acetylcholine in the cerebral cortex. First, a host of studies have revealed that drugs which interfere with the action of acetylcholine in the brain can produce in young individuals the memory impairments, resembling those in Alzheimer's Disease. Second, measurements of the enzyme that forms acetylcholine have revealed profound reductions of its activity in the cerebral cortex and related structures in individuals who have died with senile dementia. Investigators have also demonstrated that the neurotransmitters contained in a number of other neurons located within the cerebral cortex are significantly unaffected in Alzheimer's Disease. Accordingly, the chemical deficiency in acetylcholine-utilizing neurons in the cerebral cortex appears to be relatively selective in Alzheimer's Disease. Until recently, the source of cholinergic innervation to the cerebral

cortex remained unclear. In a series of dramatic studies at Johns Hopkins University carried out by PHS grantees Joseph Coyle, Dr. Mahlon Delong, and Dr. Donald Price, it was demonstrated that the acetylcholine neuronal fibers regulating the cerebral cortex come from a group of neuronal cell bodies located in the base of the forebrain in an area known as the nucleus basalis. Selective damage of this area of the brain reproduces in experimental animals the chemical abnormalities in the cerebral cortex observed in senile dementia. Examination of the brains of individuals who died with Alzheimer's Disease revealed that this group of neurons died off selectively.

While the acetylcholine-releasing neurons in the nucleus basalis are not the only neurotransmitter systems affected in senile dementia, nevertheless, they are the most consistently and severely damaged identified neuronal population. These findings are highly significant, and confirm the hypotheses of other investigators,* who are actively testing the hypothesis that enhancement of acetylcholine neurotransmission in the brain might reduce the symptoms of Alzheimer's Dementia. (*A selective sample of these projects are described under Section IV, on Treatment Studies).

Ongoing studies are also evaluating other hypotheses regarding the cause and progression of Alzheimer's Disease. The work of Lissy Jarvik, for example, at UCLA Medical Center, is evaluating whether patients with Alzheimer's Disease have a higher frequency of genetic abnormalities and of immune system changes than do older individuals diagnosed with depression or with multi-infarct dementia. Her study will also determine whether such changes can be detected in the first degree relatives of Alzheimer's patients.

In the Intramural program, a series of studies of the genetic transmission of "Alzheimer's Disease" to keep the nomenclature consistent are underway, using a computerized mapping technology which automatically detects protein or gene abnormalities (polymorphisms) in the blood or skin cells. The investigators hope to find errant proteins which might be used as markers in screening for persons genetically predisposed to develop the disease. Additional studies are examining the contribution of aluminum in the development or course of the disease.

III. How Can Alzheimer's Disease be Identified?

Clinical research remains complicated by the fact that the state-of-the-art continues to demand that the diagnosis of Alzheimer's Disease in the living patient be formulated solely on the basis of exclusionary criteria. That is, the diagnosis, at present, can only be reliably formulated if all other possible causes of cognitive impairment have systematically been ruled out. Accordingly, a variety of important studies are presently underway at NIMH, which are attempting to discover new biological or behavioral markers capable of reliably indicating the presence in older persons.

Some highlights of this work include, for example, studies of the electrophsiologic changes which accompany the progressive dementing process. The work of Patricia Prinz, at the University of Washington (Seattle), is illuminating the nature of the sleep pattern and circadian rhythms in Alzheimer's patients, in an effort to derive more precise indicators of the presence and course of disease. Similarly, studies by Bert Kopell, at Stanford University, and Leonard Berg, at Washington University (St. Louis), have focused on studies of event-related brain potentials, in the hope of using increases in the latency of P-300 as diagnostic markers for Alzheimer's Disease.

In differential diagnosis, studies of memory and cognition are also important, not only because we know little about the clinical course of Alzheimer's Disease, but because mood disorders appear to be early correlates of dementing illness (although they may also closely mimic organic impairment). The more that is known, with precision, about the specific effects of the illness on parameters of memory and mood, the more effective neuropsychological and behavioral tests can be. At the Texas Research Institute of the Mental Sciences in Houston, George Niederehe is studying different forms of memory impairment in Alzheimer's patients and in elderly diagnosed with depression, with an aim to discovering which memory mechanisms are differentially impaired. Using a different approach, Bart Vrtunski, at Case Western Reserve University in Cleveland, is examining the nature of decision-making and information processing in individuals with Alzheimer's Disease to determine whether the locus of the cognitive impairment can be differentially traced to problems in sensory input systems, stimulus eroding, response selection, or response execution stages of choice reaction-time behavior. He hopes to emerge with a battery of empirically-based memory tests which will sharpen the precision of Alzheimer's diagnoses. Neuropsychological studies in the intramural program have distinguished the nature of memory loss in Alzheimer's from that seen in Korsakoff's Disease and depression; patients with Alzheimer's have been found to have little access to semantic memory--previously acquired knowledge-- and therefore have significant difficulty organizing and encoding ongoing events. In contrast, Korsakoff's patients can assess previously acquired knowledge, but show a gross impairment of recent (episodic memory). While depressed patients also show episodic forms of memory failure, these are typically associated with tasks requiring sustained

attention. Findings such as these can go far toward enhancing our understanding of the nature of the cognitive dysfunction in Alzheimer's Disease, and toward assisting in the formulation of new and better approaches for diagnosis and accurate assessment.

Because the diagnosis of Alzheimer's Disease in the living patient must be formulated solely on the basis of exclusionary criteria, it is critical that the diagnostic yield and cost effectiveness of a broad spectrum of diagnostic procedures be systematically evaluated. Given the growing concern with the rapidly escalating costs of medical care, questions have been raised as to whether the costs of providing older persons suspected of having dementia with exhaustive, comprehensive medical evaluations, running into the $1,000 range, are really worth the outcome. It has also been suggested that such costs are more than compensated for by reductions in the cost of inappropriate treatment or inappropriate placement in nursing homes or long-term facilities. Eric Larson, at the University of Washington, Seattle, is currently evaluating the cost effectiveness of various components of a thorough evaluation designed to detect reversible causes of dementia in the elderly. The findings will result in the formulation of a set of predictors which will yield the most effective differential and prognostic information

The differential diagnosis between severe depression and Alzheimer's Disease is commonly acknowledged to be one of the most difficult and problematic in all of geriatrics. This issue constitutes a significant problem, not only because depression appears to be a common early correlate of dementia in senescence, but also because it may closely simulate a dementing syndrome. The importance of formulating an accurate diagnosis in the elderly is critical,

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especially in cases of depression mistaken for dementia, where the failure to treat may result in suicide. Although the evidence is clear in suggesting that older persons with depression complain more about their memory than do aged persons with normal mood, the literature is controversial on whether or not individuals with depression actually manifest a measurable memory deficit.

The nature of the association between memory impairment and possible cause and effect in this equation remains questionable. For example, does perceived memory change cause a change in mood state, or is the depression itself responsible for the decline in memory? Is the problem simply amplified by memory complaints? Most importantly, are there qualitative differences in memory processes between depressed and demented patients that might assist in the distinction between these conditions? This research project will clarify these questions. Evidence of differential effects on these separate memory processes as a function of diagnostic classification may lead to insights regarding the basis of memory problems. The relationship between memory measures and clinical outcome will hopefully yield immediate practical applications by providing possible prognostic indicators.

IV. What are the Most Important New Leads Regarding Treatment and Management of Alzheimer's Disease?

Over the past decade, our understanding of the complex processes involved in brain function has advanced tremendously. Particularly important in this respect is the compelling evidence which has accumulated from a number of lines

of research suggesting that Alzheimer's Disease is associated with the impaired function of neurons which utilize the chemical messenger acetylcholine in the cerebral cortex. Intramural scientists have demonstrated that drugs which interfere with the action of acetylcholine in the brain can produce in the young cognitive impairments that resemble those seen in Alzheimer's Disease. Scopolamine, for example, which antagonizes the neurotransmitter acetylcholine, has been found to specifically impair the encoding consolidation and retrieval of memories. On the other hand, drugs that enhance acetylcholine activity (e.g. lecithin and anticholinesterase) appear to produce moderate improvement in memory in some Alzheimer's patients. Currently a number of studies exploring these issues are being supported. These include, for example, a study of lecithin and piracetam (by Steve Ferris, at New York University), in which provocative results from animal studies by Bartus have led to an open clinical trial in eight humans, of whom three to four showed some signs of improvement in cognitive function. A new project represents an effort to determine whether this finding can be maintained in a double-blind control trial.

Suzanne Corkin at the Massachusetts Institute of Technology, is investigating a variety of cholinergic interventions including lecithin and physostigmine, a cholinesterase inhibitor. The study is based on work by intramural scientists and others, showing that physostigmine exerts a facilitating effect on learning and memory. Other studies carried out by Tinklenberg, at Stanford, include investigations of the efficacy of neuropeptides in the treatment of Alzheimer's Disease, including ACTH 1 - analogues of the neurotransmitter vasopressin (DDAVP). In evaluating these agents, intramural scientists have

found DDAVP to be associated with a small improvement in learning and recall. These improvements, however, were found to be much greater for depressed and normal patients, suggesting that progressive and irreversible destruction of brain cells in Alzheimer's Disease severely limits DDAVP's efficacy for dementia patients. Of interest over the past year has been the work of Barry Reisberg and Steven Ferris, at New York University, in focusing on the effects of the opioid antagonist, naloxone, in the treatment of patients with Alzheimer's Disease.

Neuroscience advances over the past decade have revealed the existence of natural opium and morphine-like substances in the human brain and, to some extent, throughout the body. These substances known as the endorphins and enkephalins, are believed to have important effects on brain functioning. Naloxone blocks the effects of these natural opium-like substances. Preliminary findings by these investigators suggest some positive effects in some patients treated with naloxone, which appear to last for 1 to 3 weeks following injection. More extensive studies of this agent are presently underway. It is possible that the action of naloxone may result from a favorable interaction with impaired acetylcholine-containing neurons. While these represent only initial findings, they are encouraging and indicate that further research may bring us closer to having a clinically effective treatment for this major illness.

Because of the frequency with which mood disorders appear concomitantly with Alzheimer's Disease, a number of investigators are also focusing on the treatment of depression in the face of chronic, progressive, dementing brain disease. For example, Burton Reifler, at the University of Washington in

Seattle, is studying elderly patients with dementia, both with and without depression, to determine if they differ with respect to antecedents and response to treatment with a trial of tricyclic antidepressants. Do the two groups have different outcomes regarding cognitive function? Ira Katz, at the Albert Einstein College of Medicine, is evaluating the presence, nature, and treatment of mood disorder in Alzheimer's patients, in an effort to better understand the course and outcome of pseudodementing and true dementing states, especially when the latter appear concomitantly with mood disorders.

Studies evaluating the utility of behavioral interventions are just beginning, and that area, too, appears to be rapidly developing. In an initial study Steven Zarit, at the University of Southern California, evaluated a variety of operationalized behavioral treatments for elderly persons diagnosed with Alzheimer's Disease who were living in the community, in an effort to specify the differential efficacy of specific behavioral organizing strategies, mnemonic techniques, and interpretive approaches. He found that in the form in which these approaches are currently conceptualized, they appear to have minimal impact on memory, but tend to lessen feelings of depression in the mildly impaired. The recent advances in our understanding of the basis for senile dementia result from a close interaction between neuroscientists and clinicians. Information derived from basic neurobiologic research is now rapidly being utilized to analyze disorders of the human brain. While it would be misleading to suggest that a cure for senile dementia is upon the immediate horizon, nevertheless, it is clear that over the last several years we have moved from ignorance and therapeutic nihilism to a position of asking informed questions concerning the causes and treatment of this devastating disorder.

V. What is the Impact of Alzheimer's Disease on the Family?

Along with growing concern regarding the serious economic cost of this disorder on the fabric of American life, is the rapidly emerging awareness regarding the devastating emotional impact that dementing illnesses exert on family members and relations. Family members caring for Alzheimer patients appear to be subjected to severe stresses and may be at especially high risk for depressive reactions. The inability to alter the course of the disease, the nature of the demanding care required, and the inevitable bereavement to be faced make such reactions especially probable. In a study of stress vulnerability in Alzheimer's patients' families, Joseph Becker, at the University of Washington in Seattle, is presently studying the predictive power of two specific models of depressive vulnerability in these families. In a related project, Adrian Ostfeld, at Yale University, is examining the consequences of spousal illness and death on a surviving partner.

Further research in this area is under way at the Texas Research Institute of Mental Sciences in a clinical and longitudinal study of relationships between family systems and dementia. The study is examining patterns of stress in community caregivers who provide home care to elderly relatives with progressive chronic brain disease. Since dementia is seen as a process which affects all members of the family unit, the study will evaluate how family system characteristics mediate the impact of the disease on caregivers and patient alike. Measures of social role functioning, physical and mental health, and subjectively experienced strain over time will be obtained from the primary caregiver and other family members. A variety of current and historical factors in the family system are bing assessed as potential predictors of the disease's

impact on the other family members, and reciprocally of the patient's own maintenance of function over time. Interpersonal factors, such as traditional family loyalties and past relationship between patient and caregiver, characteristics of the extrafamilial social network, and elements of family cohesion and adaptability, are also being investigated. The study will help to clarify how the family system influences changes in both caregivers and dementia patients over the progressive course of chronic brain disease. Coping patterns and other critical factors which predict better outcomes will be identified.

Other studies include the work of Steven Zarit, at the University of Southern California, who is evaluating the differential efficacy of family and group counseling for caregivers of patients with Alzheimer's Disease, as a means of reducing the burden of care, and of making home placement feasible for families who desire it. In the context of the Epidemiologic Catchment Area Project, Terri Sluss, of Johns Hopkins University, in collaboration with Drs. Ernest Gruenberg and Morton Kramer, is assessing the extent of emotional and economic burden on the caregivers of Alzheimer's patients in a stratified sample of the population in Baltimore. Joanne Steuer, at the UCLA Medical Center, is systematically studying the impact of support groups for caregivers of elderly patients with Alzheimer's Disease, in an effort to determine their effect of levels of depression, anxiety, and feelings of burden in family members. Ideally the results of this family oriented research will have important applications for a variety of service providers and particular usefulness to such key consumer groups as the Alzheimer's Disease and Related Disorders Association.

In summary, while the problems in understanding the causes and effects of Alxheimer's Disease, in estimating its distribution in the population, and in devising effective treatment strategies for its amelioration remain great, significant progress has been made in moving us from a position of darkness and ignorance to one of asking focused and informed questions in the historic effort and challenge to understand, treat, and prevent this devastating and costly disorder.

National Institute of Mental Health

Fact Sheet:

Center for Studies of the Mental Health of the Aging
Gene D. Cohen, M.D., Chief

SENILE DEMENTIA (ALZHEIMER'S DISEASE)

What It Is:
What It Is Not:

Senile dementia is not a normal part of aging. It is not something that inevitably happens in later life. Rather, it is a disease of unknown cause (hardening of the arteries or arteriosclerosis, contrary to popular belief, is not the cause) that affects only a small percentage of older adults. It is the exception, rather than the rule, in old age. Only about 5 to 6 percent of older persons develop senile dementia. This, of course, still amounts to a lot of people--over a million, since there are more than 22 million in the 65-and-older age group. When senile dementia does occur, its onset is usually in the seventies and only rarely before age 65. When the disease occurs before age 65, it may be called presenile dementia. The term "Alzheimer's Disease" is often used to describe senile dementia, whether it occurs after or before age 65. Senile dementia is at present known to be an incurable disease in which abnormal changes in the tissue of the brain result in many general symptoms. Heredity plays a small role in the disease, genetic studies showing only a slight increase in its incidence in other family members. That is, the risk of someone else in the family getting the disease is low, only a little more than the likelihood for the population as a whole.

The Symptoms and the Clinical Course of the Disease:

The onset of senile dementia is usually very slow and gradual. Over time, however, it follows a progressively serious and deteriorating course. Among the various symptoms that typically develop, none is unique to senile dementia. Many other conditions--both physical and psychological--can mimic senile dementia at its various stages. It is therefore essential for suspicious changes to be thoroughly evaluated before they become inappropriately or negligently labeled senile dementia.

Problems of memory, particularly recent or short-term memory, are common in the early stage of the disease. For example, the individual may, on repeated occasions, forget to turn off the oven or may not recall which of the morning's medicines were taken. Mild personality changes, such as less spontaneity or a sense of apathy and a tendency to withdraw from social interactions, occur early in the illness. As the disease progresses, problems in abstract thinking or in intellectual functioning take place. The individual may begin to have trouble with figures when working on bills, with understanding what is being read, or with organizing the day's work. Further disturbances in behavior, such as being agitated, irritable, quarrelsome, and less neat in appearance, may also be seen at this point. Later in the course of the disease, the afflicted

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may become confused or disoriented about what month or year it is and be unable to describe accurately where they live or to name correctly a place being visited. Eventually they may wander, not engage in conversation, become inattentive and erratic in mood, uncooperative, incontinent with loss of bladder and bowel control, and, in extreme cases, totally incapable of caring for themselves.

Though the changes just described represent the general range of symptoms for senile dementia, the specific problems, along with the rate and severity of decline, vary with the individual. Also, the reaction of the individual to his illness, the capacity to cope with it, varies, depending on what the lifelong personality has been like and on the stress caused by the immediate environment. Thus, other problems, such as depression, severe uneasiness, and paranoia or delusions, may result from the disease. These associated symptoms or reactions, however, can often be alleviated by appropriate interventions.

The Problem of Accurate Diagnosis: Other Disorders Confused with Senile Dementia:

Senile dementia is one of the most overdiagnosed and misdiagnosed disorders of the mind. Part of the problem, already alluded to, is the many other disorders whose symptoms resemble those of senile dementia, especially head injuries and conditions that cause irritation to brain tissue. The crucial difference, though, is that many of these disorders--unlike that of senile dementia--may be stopped, reversed, or cured with appropriate treatment. But first they must be identified, not dismissed as senile dementia. Conditions in general that bring about abnormal and identifiable changes in brain tissue are called Organic Brain Syndromes (OBS). OBS represents a broad category of diseases and includes senile dementia. Other OBS disorders that can cause problems like those of senile dementia, but at the same time might be reversible, include the following:

A. Trauma: Injuries to the head.

B. Infections: Especially viral or fungal infections of the brain.

C. Metabolic: Thyroid problems, nutritional deficiencies, anemias, etc.

D. Drug Side Effects: Wrong dosages of drugs or combinations with certain other drugs which cause adverse side effects; also alcohol.

E. Toxic: Carbon monoxide, methyl alcohol, etc.

F. Circulatory: Strokes, heart problems, etc.

G. Tumors: Any type within the skull.

H. Neurological: Normal-pressure hydrocephalus, multiple sclerosis, etc.

In addition to these organic brain syndromes, several psychiatric problems can also be confused with senile dementia. A classic example here is with "pseudo-dementia." Pseudo-dementia is actually a severe form of depression which, in the elderly, appears identical to senile dementia, but pseudo-dementia, like other depressions, can be reversed.

Questions about memory or forgetfulness cause too many people to jump to stereotypes about "senility." The word "senility" itself is misleading. It is not a medical term and has no agreed-upon meaning. Rather, it seems to be loosely used to describe vague concepts about changes in later life, especially memory changes. But many memory changes are only temporary, such as those that occur with bereavement or any stressful situation that makes it hard to concentrate. In fact, older people are often accused or accuse themselves of memory changes which are

not really taking place. If a person in his thirties misplaces keys or a wallet, forgets the name of a neighbor, or calls one sibling by another's name, nobody gives it a second thought. But the same forgetfulness for people in their seventies may raise unjustifiable concern. Moreover, rigorous studies on intelligence in later life show that healthy people who stay intellectually active maintain a sharp mind throughout the life cycle.

The Importance of a Comprehensive Medical Evaluation:

Because of the many other disorders that can be confused with senile dementia, a comprehensive medical evaluation is essential for a diagnosis of symptoms that look like those of senile dementia. Such an assessment should include a thorough general medical workup in addition to extensive neurological and psychological studies. The family physician can be consulted about the best way to get the necessary examinations.

Treatment:

Several areas that need to be considered with regard to treatment for senile dementia include treatment for the disease itself, intervention to assist the individual with his adjustment and psychological reaction to the illness, attention to what can be done to improve conditions in his immediate environment and living arrangement, and support for his family.

As for the disease itself, there is no available treatment at present that can cure it, reverse it, or stop its progression. Several drugs and techniques, such as the use of hyperbaric oxygen, have been tried but have not been successful. Indeed, some of the drugs used are not without risk. The hyperbaric oxygen technique can be expensive and has been shown to be of no value. Careful and expert consultation should be sought whenever the use of new or experimental drugs or techniques is considered. At present, then, the treatment approach to the disease itself is one of helping the afflicted individual through the course of the disorder to maintain as much comfort and dignity as possible. On the other hand, treatment can have a positive impact on other forms of organic brain syndrome and on various psychiatric disorders which are confused with senile dementia.

There are several interventions that can assist the person with senile dementia who is experiencing disturbing psychological or adjustment reactions to the illness. Such interventions include emotional support from the family, at times supplemented by therapy from a mental health professional. The judicious use of drugs is often helpful, especially when delusions or severe agitation are present. There are also specialized behavioral techniques to help the individual use to the maximum his reserve strengths and potentials. Some clinicians believe that such techniques (for example, reality orientation) might slow the progression of the disorder itself, but this remains a controversial issue.

Altering the individual's immediate environment can be helpful from several perspectives. There is the matter of safety, as in the need to protect the person from wandering toward a stairway and subsequently falling. There is the matter of lowering the frustration level, such as placing different cues in the immediate environment to combat memory loss and to reduce resulting stress and disorganization. There is the matter of finding the most protective but least restrictive setting for care which at some point may involve a move away from home to a care facility well-equipped to deal with those who have senile dementia.

Not to be overlooked is the need for assistance to the family as a whole. Particularly when the person with senile dementia is staying with the family, a homemaker or other aide might be sought. As the disease progresses, the family often experiences tremendous stress and pain at seeing unsettling changes in their loved one, and they

commonly feel guilty over not being able to do enough. To the extent that family members can offer emotional support to each other and perhaps seek professional consultation, they will be better prepared in helping their loved one manage the illness and in coming to know the limits of what they themselves can reasonably do.

Outlook:

As a final point, national and international interest in studies on the cause and treatment of senile dementia is rising dramatically. In the United States, three Federal programs are actively stimulating research proposals in this area. The National Institute of Mental Health (NIMH), the National Institute on Aging (NIA), and the National Institute on Neurological and Communicative Disorders and Stroke (NINCDS) have collaborated in developing important new programs aimed at answering more questions about this very serious disease.

This material is derived from an interview with Gene D. Cohen, M.D., on the television program "Over Easy" in February 1979. Dr. Cohen is Chief, Center for Studies of the Mental Health of the Aging, Division of Special Mental Health Programs.

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Senator GRASSLEY. Thank you, Dr. Pardes.

Would you proceed, Dr. Ringler?

Dr. RINGLER. Thank you, Mr. Chairman, for this opportunity to testify with my colleagues. I am pleased to present an overview of the National Institute on Aging's program on Alzheimer's disease. Since the inception of the National Institute on Aging, we have concentrated heavily on the positive aspects of aging, with certain broad objectives in mind, such as developing a better understanding of normal aging and promoting health and effective functioning among the elderly. Our public statements on dementia in the elderly have emphasized that only about 5 percent of the 26 million Americans over 65 years of age suffer the cognitive impairment formerly thought to be a normal part of old age.

However, a closer inspection of the statistics reveal a problem of far more significance. In order to give you some sense of these statistics, I would like to cite three or four of them for you.

Between the ages of 60 and 80, the risk of developing dementia doubles about every 5 or 6 years. Currently, one-third of the entire population in developed countries will live to age 80 and beyond, where there is an estimated 20 percent chance that a person will have a serious, irreversible dementia. Beyond age 80, it is assumed that the risk continues to increase at about the same general rate. This observation, coupled with the fact that by the year 2000—which, after all, is just some 17-years down-the-road—it is estimated there will be twice as many people in the world at age 80 as there were in 1970. This provides an alarming insight into the dimensions of the disease that is being discussed at these hearings.

In keeping with the legislative mandate of the National Institute on Aging, which directs that the Institute foster scientific research not only on the normal processes of aging but also on the diseases and other special problems and needs of the elderly, we have placed a very high priority on the program area related to Alzheimer's disease. In 1976, when the programs of the Institute were first being constituted, less than $1 million from the NIA budget was spent on research in this area. In 1983, this figure is expected to exceed $11 million, in part due to expanded programs of extramural grants and awards related to Alzheimer's disease and in part due to the addition of the Institute's epidemiology, demography, and biometry program and the intramural program in neurosciences, both of which have major emphasis in this area.

Until recently, most experts in the scientific and medical community believed that Alzheimer's disease was a rare neurological disorder which typically occurred in persons in their late forties and early fifties. At the same time, it was generally accepted that forgetfulness, confusion, and other senile-like symptoms were a normal part of aging. In 1977 and 1978, two major international conferences were sponsored by the three Institutes represented here this morning. These conferences focused on the pathological and clinical relationships between senile brain disease and Alzheimer's disease. In 1979, NIA sponsored a Technical Consensus Conference on treatment possibilities for mental impairment in the elderly, which helped focus attention on the difference between normal aging and dementia. As a result of these and other efforts,

Alzheimer's disease is today recognized as the most common cause of severe intellectual impairment in older individuals.

Because of studies during the past decade, considerable information is now available about Alzheimer's disease and its possible causes. Much of this research has been highlighted in my own statement for the record and in the statements of my two colleagues. Our three institutes now share in the funding of an extensive program of both extramural awards and intramural research.

Dr. Goldstein has provided an excellent overview of the neurobiology of the disease and its possible causes. NIA grants and awards in this area now total some $9 million. In addition, the National Institute on Aging's Laboratory of Neurosciences, under the direction of Dr. Stanley Rapoport, has been involved in an intensive investigation of brain metabolism and normal aging and dementia. During 1982, the Institute established a clinical research program at the Warren G. Magnuson Clinical Center at the National Institutes of Health and a series of activities focusing primarily on Alzheimer's disease and related neuropathological diseases of the elderly. Dr. Rapoport and his colleagues have examined some 55 men, aged 21 to 83, and they find that the healthy aged brain appears to be as active and efficient as the healthy young brain. They have also looked at a group of some 12 Alzheimer patients and have found depressed glucose metabolic rates relating to the severity of the disease.

The epidemiology, demography, and biometry program of the National Institute on Aging is also moving forward with studies on the incidence, prevalence, natural history, and risk factors associated with Alzheimer's disease. In one study, investigators will delineate the course of intellectual decline and general health in a group of Alzheimer victims and normal controls. In the second study, researchers are taking a closer look at the participants in the Framingham heart study who have developed dementia. Extensive data on these subjects may help identify important factors associated with the development and course of Alzheimer's disease.

Finally, in keeping with its legislative mandate, in 1981, NIA prepared a progress report on Alzheimer's disease research, which was made available to the Congress and all other interested parties. We have also prepared a 1983 progress report summarizing the activities of the Public Health Service in this area. I would like to leave a copy of this report with you for the record, if I may.

Senator GRASSLEY. Thank you very much. We will receive it.

[The progress report referred to and the report summarizing the activities of the Public Health Service follows:]

PROGRESS REPORT ON SENILE DEMENTIA OF THE ALZHEIMER'S TYPE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

Prepared for the
Senate Committee on Appropriations
February 1983

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Thomas E. Malone, Ph.D.
Deputy Director, NIH

February 1983

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PROGRESS REPORT ON SENILE DEMENTIA OF THE ALZHEIMER'S TYPE

Executive Summary

Senile dementia of the Alzheimer's type (SDAT), the major form of old age "senility," is the cause of serious confusion and forgetfulness in some 1,500,000 elderly Americans and a probable contributor to the institutionalization of as many as half of the more than one million elderly in long-term care facilities. Given the high incidence and enormous cost of SDAT, the Senate Committee on Appropriations has requested the following report on the state of science of this disease.

Since 1976, when the interest of three Federal research organizations --the National Institute on Aging, the National Institute of Neurological and Communicative Disorders and Stroke, and the National Institute of Mental Health--focused on the prevalence and possible causes of this disorder, government research activities on the dementias of aging have increased by more than 500 percent.

A major inroad came when it was demonstrated that SDAT is a neurological disorder and not a normal consequence of aging. Since then, some studies have looked at the biological mechanisms of SDAT, in particular the role and chemical composition of structures that irreversibly alter aging brain cells and play a major role in Alzheimer's type dementia.

Other scientists have employed a variety of methods to investigate what causes SDAT. Research on certain well-established chemical changes in the SDAT brain have become more intriguing recently because of evidence of the selective destruction of cells in a part of the base of the brain which provides these chemicals to higher brain regions. Studies on the contribution of aluminum to the disease's development have been linked with a new environmental hypothesis. Scientists have furthered their understanding of the effects of viral infections on the central nervous system in diseases similar to SDAT. Genetic studies have shown a clustering of Alzheimer cases in some families although no consistent pattern of genetic transmission has been demonstrated.

Research is just beginning to address whether psychosocial factors may contribute to the causes or development of SDAT. To date, behavioral sciences research has focused mainly on the search for definitive diagnostic tests, on linguistic behavior in relation to brain function and dysfunction, and on special supports needed by families of victims.

On the basis of early findings of biomedical, social, and behavioral studies, a number of scientists are developing projects aimed at improving care and treatment for SDAT victims. Clinicians need a more sensitive and reliable diagnostic test or some kind of "marker" which will detect the disorder in its earliest stages. Other clinical researchers are attempting to compensate for established declines in brain chemistry as a way of treating the serious symptoms of SDAT. This research is set in the context of major advances in the field of neuroscience, including advances, aided by computer technology, in the ability to view and understand the workings of the living human brain.

The following report on SDAT provides a brief overview of the "Role of Technology", "Biological Mechanisms of SDAT", "What Causes SDAT?", "Psychosocial Research", "Clinical Research", and "Intramural Activities".

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INTRODUCTION

In its report on the Fiscal Year 1983 budget for the Department of Health and Human Services, the Committee on Appropriations stated:

> "Significant progress has been made toward improved understanding of senile dementia, a condition of high incidence among the elderly population and of enormous social cost. Approximately 3 to 4 million elderly Americans suffer from some type of dementia. Some 1,500,000 of these have senile dementia of the Alzheimer's type with intellectual deterioration and inability to carry out the normal tasks of daily living...The Committee is anxious to see that Alzheimer's disease research efforts now underway at various Institutes and other agencies of government have strengthened coordination and cooperation. The Committee directs that, prior to next year's hearing, a report be submitted to the Committee on the state of science of Alzheimer's disease, as well as on the efforts undertaken to ensure better coordination among the Institutes and other agencies of government." (Senate Report No. 97-680, page 55)

The following report has been prepared by the National Institutes of Health of the Department of Health and Human Services in response to this request.

BACKGROUND

Senile dementia of the Alzheimer's type (SDAT) is indeed a disease of catastrophic proportions. Now regarded as the major form of old age "senility," it is a surprisingly common disorder that affects the cells of the brain. While experts formerly believed that Alzheimer's disease only occurred in persons under 65, this disorder is now recognized as the most common cause of severe intellectual impairment in older individuals. Whether the classic form of Alzheimer's disease, which was first described in a middle-aged adult, is identical in cause, mechanisms, and course to senile dementia of the Alzheimer's type is a matter of some controversy. In this paper, Alzheimer's disease refers to cases of early onset, SDAT refers to cases which occur after age 65, and Alzheimer's type dementia is used collectively to imply both types.

The major debilitating symptoms of SDAT include serious forgetfulness--particularly about recent events--and confusion. At first, the individual experiences only minor and almost imperceptible symptoms that are often attributed to emotional upsets or other physical illnesses. Gradually, however, the person becomes more forgetful and this may be reported by anxious relatives. The person may neglect to turn off the oven, may misplace things, may recheck to see if a task was done, may take longer to complete a chore that was previously routine, or may repeat already answered questions. As the disease progresses, memory loss and such

changes in personality, mood, and behavior as confusion, irritability, restlessness, and agitation, are likely to appear. Judgement, concentration, orientation, writing, reading, speech, motor behavior and naming of objects may also be affected. Even when a loving and caring family is available to give support, the victim of SDAT is most likely to spend his or her last days in a nursing home or long-term care institution. At this time, there is no cure.

COORDINATION

Since 1976, Alzheimer's disease has become a major priority for Federal research. The attention paid to this issue has resulted in increased interest among the scientific community and in growing cooperation and coordination among the Federal research agencies responsible for studies on aging, neurological disorders, and mental health. Cooperative efforts among the National Institute on Aging (NIA), the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), and the National Institute of Mental Health (NIMH) include scientific collaboration among intramural scientists in the different institutes, joint sponsorship of conferences and workshops, joint issuance of a program announcement, collaboration on assignment of research grant applications, and several interagency agreements. Specific examples include:

-- Collaboration Among Intramural Scientists. Although the NIA clinical research program has only been in existence since September 1982 when the first Alzheimer patients were admitted to the NIH Clinical Center, there have already been several cooperative activities. Currently NIA, NIMH, and NINCDS scientists are involved in a collaborative study of cerebrospinal fluid concentrations of a variety of neurotransmitters, proteins, and neuropeptides possibly involved in normal aging and dementia. In a second collaborative study, NIMH and NIA scientists are assessing motor coordination and motor function in healthy aged subjects and in demented individuals.

-- Interagency Agreements. The NIA has two interagency agreements with the National Heart, Lung, and Blood Institute to study functional disability and dementing illness in the participants of the longitudinal Framingham Heart Study. Participants in this study have had 17 highly comprehensive examinations over a 30 year period. These agreements allow the NIA to have access to this data, to follow the population as it ages, to establish prevalence rates, and to identify possible causes of specific illnesses.

The NIA has an interagency agreement with the NIMH to estimate the prevalence of senile dementia in a New Haven community population of 3,000 persons who are 65 years of age or older. Preliminary results have already generated useful information on developing a screening instrument for dementia.

The NINCDS has an interagency agreement with the NIMH to provide

data on the incidence and prevalence of Alzheimer's disease, the history and progression of Alzheimer's disease, and on the economic and social impact of Alzheimer's disease as it affects individuals, their families, and friends. Information thus gathered might provide insight not only on intervention modalities that would prevent or alter the course of the disease but also on optimum utilization of available resources for adequate allocation of services as needed.

-- The NINCDS intends, under a joint agreement with the NIMH, to amplify the operation of a neurospecimen banking facility that has been in operation for three years, during which specimens of human brain, spinal cord, peripheral nerve, muscle, and cerebrospinal fluid were solicited, collected, dissected, stored, and distributed to various neuroscience researchers, free of charge, to meet their needs in studying a variety of neuropsychiatric disorders including Alzheimer's disease and many others. Sixty scientific articles have already been published as a result of research using this Brain Bank's donor specimens.

-- Joint Funding of Conferences. Over the years, cooperative efforts among the NIA, NINCDS, and NIMH have resulted in a variety of important national and international conferences on the prevalence, causes, and possible treatment of SDAT; on the diagnosis of dementia in its curable and incurable forms; and on the ethical implications of research on patients whose capacity to speak for themselves has been compromised.

One particularly successful cooperative venture of the Institutes--a meeting of self-help family support groups--catalyzed the formation of the Alzheimer's Disease and Related Disorders Association (ADRDA). Since 1979, ADRDA has developed into an organization which 1) offers counsel and emotional support to affected families through nearly 60 chapters and more than 300 family support groups, 2) bolsters the NIH/ADAMHA research missions in giving small grants to young investigators and investigators new to the field of dementia research, and 3) educates members as to the need for scientific research and the importance of confirming the diagnosis of Alzheimer's disease by autopsy.

-- Joint Issuance of Program Announcement. Program announcements are published in the NIH Guide for Grants and Contracts to encourage investigators to submit research grant applications in selected areas of interest. In May 1981, the NINCDS and the NIA jointly announced the Institutes' interest in supporting research on "Alzheimer's Disease and Other Related Dementias of Aging," particularly in the areas of differential diagnosis, clinical and/or pathological studies, cerebral circulation and metabolism, neurochemistry, neuroendocrinology, genetics - population studies, immunology - virology, and animal and other model systems.

-- Collaboration on Assignment of Research Grant Applications. The NIA and the NINCDS are engaged in continuing discussions to clarify their respec-

tive roles in the support of research on senile dementia of the Alzheimer's type. Representatives of each Institute have agreed upon several general principles to ensure the appropriate and equitable assignment of pending grant applications. An agreement dated 12/21/81 is currently in effect. Preliminary discussions have been carried out between NIA and NIMH staff to adopt similar guidelines. There is also free and open exchange of pending grant applications so that the Institute not assigned the grant can request dual assignment. This sets the stage for transfer of pending grant applications from one Institute to another in the event that reassignment is appropriate or that the primary Institute is unable to pay a meritorious pending grant application because of budget limitations.

-- Scientists Receiving Grant or Other Support From More Than One Institute. In some instances, scientists at universities and medical centers are awarded grants from more than one Institute. In other instances, intramural scientists from one Institute are collaborating with grantees from other Institutes. The following report includes several examples of each phenomenon: a neuropathologist and neurologist at the McLean Hospital is studying the role and chemical composition of proteins in normal and SDAT brains (NIA) and is the current recipient of a Teacher Investigator Development Award (NINCDS) to establish a training program in theoretical and experimental aspects of protein chemistry as these relate to abnormal proteins in human disease; investigators from the Johns Hopkins University are studying changes in the basal forebrain in aging and dementia (NIA), the selective destruction of nerve cells in Alzheimer's dementia (NINCDS), and the significance of this cell loss in the development of neuropsychiatric disorders (NIMH); an NIA grantee at the University of Vermont is collaborating with NINCDS intramural scientists in a study of metal deposits in the brains of dementia victims; scientists at the University of California at San Francisco are attempting to characterize the agent responsible for the development of two model disorders, scrapie (NINCDS) and Creutzfeldt-Jakob disease (NIA); a group of investigators at the Albert Einstein College of Medicine are receiving NIA and NINCDS grant funds for a broad range of studies on dementia, including research on the structural abnormalities which characterized SDAT; the biochemical alterations in the disorder; the link between neurochemical changes in aging and dementia, changes in brain function, and the physical changes in the brain which can be measured only after autopsy; the risk factors which might lead to the development of vascular and other dementias; the chemistry of immune complexes in SDAT; learning and memory in aging and dementia; as well as a longitudinal study of 500 nursing home residents which has generated a wealth of data on normal aging and dementia through psychological evaluation and postmortem analysis.

Over the past decade, research scientists have made major advances in their studies of aging and the brain. At the same time, scientists, health professionals, policymakers, and the public have experienced a growing awareness of the impact of senile dementia of the Alzheimer's type. Against this background, scientific studies of the diagnosis, causes, nature, incidence,

prevalence, and course of SDAT have established a solid foundation for research which has improved our understanding of the disease and care for, and possible treatments of, its victims, and which may allow us to cure and possibly prevent senile dementia at some future date. Much of this has been due to the increased interest and cooperation of the NIA, NINCDS, and NIMH programs in neurology and aging.

BIOLOGICAL MECHANISMS OF SDAT

Glucose metabolism is one of three major interconnected measures of brain activity--the other two are brain blood flow and brain oxygen consumption. New noninvasive machinery which ties x-ray technology to computer technology allows simple tests of glucose metabolism and, in turn, provides a direct measure of activity in any given brain region. NIH scientists and others using positron emission tomography (PET) and a compound similar in structure to glucose to measure glucose metabolism have come up with some fascinating findings about the workings of aged healthy and diseased brains.

Using PET to scan the normal aging brain, Ranjan Duara and his fellow scientists in the NIA Laboratory of Neurosciences have found no significant age-related alterations in brain glucose metabolism. Duara and his colleagues tested 40 men, aged 21 to 83, and found this was true for some several dozen regions of the brains that they scanned. These studies suggest that the healthy aged brain is as active and efficient as the healthy young brain. Of current interest to the investigators is why their findings are inconsistent with changes known to take place in the size and weight (i.e., the number of cells) of the brain as it ages, as well as findings of other investigators who have reported drops in glucose metabolism with age, and the controversial findings which suggest that brain blood flow and oxygen consumption may or may not change with age. Future studies by Duara and his colleagues will continue to build upon and analyze the results of this work. In the meantime, the investigators' findings are beginning to provide age-related normal values for glucose metabolism in the brains of healthy men of all ages.

PET scans are also beginning to show that various parts of the brain deteriorate at different rates as Alzheimer's disease progresses. NINCDS scientists Norman L. Foster, Thomas N. Chase and their associates have demonstrated that lowered metabolic rates in different parts of the brain can be linked to Alzheimer patients' inability to perform certain physical tasks. The investigators selected 16 Alzheimer patients who suffered from varying degrees of apraxia, a loss of voluntary movement without actual paralysis, and asked the patients to mimic, pantomime, or identify 75 body movements. Patients responded with varying success; different patients have different types of difficulties in performing tasks. On the basis of these and other preliminary test results, the investigators have suggested that Alzheimer patients with brain damage on the right side have difficulty mimicking or imitating actions, while those with damage on the left side are unable to follow verbal commands. According to Foster, other factors may affect how well a patient performs a task, including the complexity of the task and whether or not the action has a purpose. This may eventually help in clinical practice as physicians

are better able to diagnose Alzheimer's type dementia and to treat patients.

* * * * *

The changes most commonly associated with SDAT occur in the proteins of the nerve cells of the cerebral cortex (outer layer of the brain) and lead to an accumulation of abnormal tangled fibers called neurofibrillary tangles. An important study of these characteristic nerve cell changes has revealed some unusual and unexpected findings. For several years, Dennis Selkoe, a neuropathologist and neurologist at the McLean Hospital in Belmont, Massachusetts, has received NIA grant support for his studies on the role and chemical composition of elements within normal and abnormal brain cells. Currently he is also receiving support from the NINCDS in the form of a Teacher Investigator Development Award. Much of his work has focused on neurofilaments, elements within the cell that are made up of long hair-like strands of protein. In SDAT, proteins like these bind together and twist into spiral-like configurations called paired helical filaments (PHF). Masses of PHFs form the characteristic neurofibrillary tangles of Alzheimer's type dementia. It is possible that these changes can be linked to cell death.

Selkoe and his colleagues have found that the proteins in Alzheimer tissue are highly resistent to standard protein solvents and that the molecules of the PHFs bind tightly together to form an extremely rigid "cross-linking" structure. This is not the first time that cross-linking has been observed in aging human tissue. Other examples include the changes that take place in the formation of cataracts. In their most recent studies, Selkoe and his colleagues have compared the mechanisms responsible for cross-linkage in the lens of the aging eye to what may be going on in the aging brain. In the lens, a particular enzyme called transglutaminase appears responsible for the binding of protein. Selkoe has recently completed studies marking the presence of this enzyme in the human brain. Furthermore, the investigators have experimentally induced the development of a rigid molecular structure—although different in form from the PHF—by adding this enzyme to normal filaments. Future studies will expand the attempt to find out what causes the formation of structures that age and irreversibly alter brain cells, and play a major role in Alzheimer's type dementia.

THE SEARCH FOR A CAUSE

In a decade marked by major advances in the fields of neuroscience and aging research, scientists have employed a variety of methods to investigate the possible cause(s) of SDAT. Studies have looked at the roles of deleterious changes in brain chemistry, trace metals, and slow-acting viruses, as well as the roles of heredity and of changes in the aging immune system.

Biochemical Studies

Since the mid 1970's, research scientists have been following the lead

of the first reports of a significant and progressive decrease in the activity of the enzyme choline acetyltransferase (ChAT) in the brain tissue of SDAT patients. ChAT is a key ingredient in the chemical process which produces acetylcholine, a neurotransmitter involved in both learning and memory. Until recently, the most exciting findings were those which showed a link between this change in neurochemical activity, and changes in both cognition (such as memory loss and disorientation) and the physical appearance of SDAT brains, particularly the number of characteristic plaques (degenerated nerve cell pieces which form around a fibrous core in the cerebral cortex). Current studies are aimed at expanding our understanding of the neurochemistry of human aging and dementia. In order to explore further the relationship between ChAT and SDAT, monoclonal antibodies to ChAT are being used to map out areas of the brain (biopsied or autopsied) where ChAT molecules are reduced or not and correlate these findings with the clinical picture of patients and normal elderly individuals.

Recent studies at the Johns Hopkins University bring us closer to understanding what causes this decline in the brain's complex chemical activity. In studying the brains of Alzheimer victims, NINCDS/NIA/NIMH grantees Donald Price and Joseph Coyle find a marked loss of nerve cells in a part of the base of the brain called the nucleus basalis. Patients with classical Alzheimer's disease have been shown to lose as many as 90 percent of these cells, while the same phenomenon holds true, to a somewhat lesser extent, in SDAT. Scientists are intrigued by the possibility of a link between this loss and the decrease in cholinergic activity: the nucleus basalis produces acetylcholine and utilizes the neurotransmitter and its enzymes in communicating with the brain's cortex via connecting pathways. It has been known for some time that aging produces a loss of cells in the brain's cortex. But NINCDS-supported investigations involving meticulous counting of nerve cells indicate that there is no major loss of cells in the brain's outer layer. Therefore, normal cell loss has never been able to explain the severe degree of cholinergic deficiency--between 75 and 95 percent--in this part of the SDAT brain. Since the loss of acetylcholine is so detrimental in Alzheimer patients, and the nucleus basalis now appears to be one of the major sources of the substance, researchers hope to learn why nerve cells of the nucleus basalis seem to be selectively destroyed in SDAT. Scientists are also interested in these findings because they indicate that brain centers innervating higher brain centers may be important in the development of SDAT.

Trace Metal Studies

A new and controversial finding reported by scientists at the University of Vermont and the National Institute of Neurological Disorders and Stroke has linked the results of two separate avenues of research on SDAT--research that suggests that aluminum may contribute to the disease's development, and research that probes the excess incidence of dementia in three separate populations.

With grant support from the NIA, Daniel Perl of the University of Vermont has extended his earlier findings of accumulations of aluminum within

the affected nerve cells of subjects showing the classic neurofibrillary tangles of Alzheimer's type dementia. In a recent collaborative study, Perl and NINCDS intramural scientists Gajdusek, Garruto, Yanagihara, and Gibbs reported high accumulations of aluminum, iron, and calcium in the brains of Chamorro natives of Guam who had died of amyotrophic lateral sclerosis (ALS) or parkinsonism-dementia. This population is adversely affected by these two chronic disorders, both of which were previously suspected to be transmitted by a slow-acting virus. For several years, Gajdusek and his colleagues at the NINCDS have been studying the possible implications of Guam's environmental deficiency in calcium and magnesium and excess of aluminum and other metals.

Researchers in the field of aging have kept a watchful eye on studies in Guam because of the similarities between the parkinsonism-dementia syndrome and Alzheimer's disease. In both disorders, there is an excessive accumulation of neurofibrillary tangles in the brains of victims that is associated with severe dementia and death.

These latest findings by Perl, Gajdusek and colleagues reconfirm Perl's earlier work in support of studies linking high concentrations of aluminum in the brain to the development of neurofibrillary tangles, as well as work of Japanese investigators in both Guam and Japan. NINCDS scientists are exploring the possibility that secondary hyperparathyroidism caused by lack of calcium and magnesium in the environment provokes an accumulation of metal ions within brain tissue.

Samples of garden soil and drinking water in Guam, as well as in parts of Japan and New Guinea that are similarly plagued by high incidences of ALS and dementia, indicate low levels of calcium and magnesium and unusually high levels of aluminum. All of these elements have similar chemical structures. Scientists have never been able to prove that aluminum alone predisposes a person to, or causes, Alzheimer's disease. It may be that high intake of aluminum over a long period of time, coupled with chronic low intake of vital minerals such as calcium and magnesium, ultimately results in a breakdown of the normal mechanisms which metabolize minerals. This, in turn, could result in what investigators find are toxic levels of these elements in the brain cells and in the walls of major blood vessels in the brain. Scientists have yet to determine how or why low intake of calcium and magnesium can lead to high levels of these elements in the brain but there appears to be a link since the same phenomenon occurs in three different high incidence areas. Perhaps the body is overcompensating for the lack of vital minerals by storing these in combination with other available trace elements in the bones. Ultimately this may lead to deposits in the central nervous system.

NIMH scientists are also involved in studies of how aluminum gains access to the brain. During the past several years, researchers at the NIMH Adult Psychiatry Branch at St. Elizabeths Hospital in Washington, D.C. have measured the concentrations of aluminum and a variety of other minerals in the hair of Alzheimer patients and their healthy spouses. Examples of these minerals are calcium, magnesium, manganese, copper, and zinc. To date, no difference in any of the minerals studied have been found between the two groups. Further, serum copper and zinc have been examined in both groups. Again, no differences have been noted.

Future studies in this area will determine whether accumulations of metals in the brain are a primary cause of Alzheimer's disease or if other factors or circumstances might combine with environmental factors to trigger the onset of chronic, but ultimately fatal, diseases of the nervous system.

Slow Virus Studies

The quest for an understanding of what causes SDAT continues with studies on central nervous system (CNS) diseases believed to be caused by slow-acting transmissable viruses.

Scrapie, a CNS disease that affects sheep, has provided a model for the study of dementing disorders in humans, including Alzheimer's type dementia. Animal models are hard to come by since dementia involves the loss of a capacity we cannot be sure animals ever had. Nonetheless, scientists are actively pursuing an animal or other model. Scrapie is similar to kuru and Creutzfeldt-Jakob disease, two rare diseases which cause progressive, irreversible dementia in humans. This fact, plus the well-established evidence that scrapie is the result of a slow-acting infectious agent, encouraged a new avenue of research on the possible causes of CNS disease in humans.

Scientists pursuing this line of research, however, have consistently failed in their efforts to identify and isolate any component of the infectious agent. Recent research at the University of California at San Francisco suggests that a protein is the vital force of the scrapie agent. NIA/NINCDS grantee Stanley B. Prusiner finds that animals with scrapie are infected by what he calls a small proteinaceous infectious particle, or "prion."

Prions have many properties which distinguish them from typical viruses. Although viruses contain nucleic acids which carry all of the information necessary for the virus to multiply and spread infection, prions may or may not contain a tiny nucleic acid. Even if prions are found to contain a nucleic acid, the scrapie infecting agent would still differ from a virus because the nucleic acid hidden in prions would be too small to fulfill its function and code for any meaningful amount of protein length.

Prusiner's work remains to be confirmed, but if it is, it might significantly alter our understanding of the nature of this virus and how it works with possible implications for CNS degenerative disorders such as SDAT.

Related Research

The National Institute of Allergy and Infectious Diseases (NIAID) conducts research on the biology and epidemiology of viruses associated with persistent and latent infections. William J. Hadlow and his colleagues at the NIAID Rocky Mountain Laboratories (RML) have studied Suffolk sheep naturally infected with scrapie virus and have outlined the main events

in the infectious process. They found the virus in such lymphatic tissues as tonsils and in the intestines of clinically normal lambs, aged 10 to 14 months, whose mothers later developed the symptoms of scrapie. As the lambs grew older, virus was found in the brains and spinal cords. These findings suggest that primary infection occurs by way of the digestive tract, either before birth from virus in amniotic fluid or after birth from virus in a contaminated environment.

Hadlow's study on scrapie may have implications for Creutzfeldt-Jakob disease, providing clues not only to its cause and development, but also to its possible links with exposure to the scrapie virus. For example, many investigators have looked for some association with eating sheep brain. But this study shows that virus is not present in the brains of young lambs, those most often used for human food, and underscores the importance of further research.

Since the central nervous system is one of the favored sites for persistent viral infections, research on these diseases may eventually provide a key to understanding currently baffling degenerative diseases such as SDAT and the dementias of aging.

Immunological Studies

NINCDS investigators at Sloan-Kettering Institute for Cancer Research, in exploring the role of the immune system in the cause and development of neurological disorders, are focusing on the interface between autoimmunity, immunodeficiency and central nervous system disease. Patients who are deficient in immunoglobulin absorb foreign proteins through their intestines thus leading to the development of circulating immune complexes. A mechanism linking autoimmunity and immunodeficiency is thus discovered and is further studied by looking at the effect of dietary intake on autoimmune and atherosclerotic cardiovascular disease, in an attempt to elucidate immunologic mechanisms in such chronic degeneration disorders as Alzheimer's type dementia and Down's syndrome.

Genetic Studies

For several decades, research on Alzheimer's type dementia has hinted that in either its early onset or senile form, the disease might be hereditary. In what amounts to a handful of studies on genetic influence, researchers have found an increased incidence of some form of dementia among parents and siblings of victims. Some studies show a slight increase; others show a considerable one over the occurrence of dementia in the general population. One researcher has suggested that Alzheimer's disease poses a greater risk to relatives than SDAT. Practically no data are available on risk to children. Briefly stated, the studies show a clustering of dementia cases in some families but no consistent pattern of genetic transmission.

Genetic research may eventually tell us whether we are dealing with one

disease or more in the presenile and senile forms of Alzheimer's type dementia. Such studies may also provide a way to diagnose dementia accurately using a "marker" for the disease. At the Brentwood VA Medical Center and the UCLA School of Medicine, Lissy Jarvik and her colleagues have found something unusual in the behavior of white blood cells taken from patients with Alzheimer's type dementia. With support from NIMH, Jarvik plans to continue to study what she describes as the "disoriented" behavior of cells from Alzheimer patients when exposed to temperatures which generally elicit a specific response from cells from healthy individuals. Future research from this laboratory will attempt to determine if this change is consistent and what causes it.

PSYCHOSOCIAL RESEARCH

Little research has so far addressed whether psychosocial antecedents or concomitants (e.g., environmental stressors, depressive states, alcoholism) may contribute to the cause or development of SDAT. To date, behavioral sciences research has focused mainly on the search for definitive diagnostic tests, including tests which will differentiate between SDAT and vascular dementia; on linguistic behavior in relation to brain function and dysfunction; and on special supports needed by families of victims.

Language Usage

General difficulties in language usage and comprehension have always been included among the symptoms of SDAT and other irreversible dementias. Now, an NIA-supported research scientist finds that specific language problems might be used to detect and diagnose various forms of dementia.

The recommended examination of an older person complaining of memory loss and confusion includes a battery of physical and neurological tests as well as certain psychological tests to detect or monitor declining skills. Commonly used tests can quickly evaluate a person's sense of time, place and self. They can also assess short-term memory as well as the person's skills at completing simple mathematical calculations, both of which are among the first clinical signs of SDAT. More and more, however, mental status tests include questions aimed at evaluating linguistic skills. A patient will be asked to name objects, exhibit comprehension of a spoken or written statement, or write a spontaneous sentence.

Kathryn Bayles, an NIA grantee at the University of Arizona, has found that asking subjects to name common household or everyday objects--such as a broom, a purse, an apple, or a telephone--can easily differentiate between moderately impaired Alzheimer patients and healthy older individuals, and in some instances can detect mild cases of SDAT. Such demands can uncover the subtle, if serious, deficiencies often masked by the residual social skills of an Alzheimer patient in early and middle stages of the disease.

Bayles study is one of several looking at the language skills of healthy aged adults and what happens to these skills when subjects suffer from

Alzheimer's type dementia, Huntington's disease, Parkinson's disease, or multi-infarct (vascular) dementia. Her results confirm that patients in all stages of dementia have difficulties expressing themselves, but also suggest that tests of language skills are sometimes more sensitive than certain psychological tests to the presence of dementia. Although her studies are not yet completed, it appears that the deterioration of language skills is more severe and more rapid in SDAT than in other forms of irreversible dementia.

As this study progresses, Bayles and her colleagues hope to develop a standard against which health professionals can measure the verbal performance of their patients. According to Bayles, tests of linguistic skills might be refined to determine the presence and severity of senile dementia and to outline interventions that might improve comprehension. She has already found a certain logic in the incorrect responses given by Alzheimer patients: moderately affected patients who cannot name a given object often will substitute a word which describes the object or the name of a similar object. At the very least, such studies might provide valuable information on the best methods for communicating with patients over the course of a disease which progressively limits communication.

Diagnosis of SDAT

What happens when an older person starts to show signs of "senility"?

With luck, someone--perhaps a relative--will realize the importance of going to a physician to find out what is causing the problem, if it is curable and, if it is not, what can be done to help. The victim's first contact with a health professional is likely to be an internist, a geriatrician, or a general practitioner. Because of the variety of conditions that can cause what is medically known as senile dementia--and also because of the wide range of symptoms--the patient may eventually consult or be examined by a neurologist, a psychiatrist, a psychologist, a radiologist and/or a social worker. In this way, the family might be exposed to the terminologies used by various specialists: senile dementia, Alzheimer's disease, organic brain syndrome, brain failure and senile psychosis. The accurate diagnosis of "senility," by whatever name, is clearly a challenge for physicians.

According to a study at the Philadelphia Geriatric Center, professionals from different clinical disciplines generally agree in the diagnosis of senile dementia. NIA grantee Samuel Granick has found that despite their dependence on the tools of their individual specialties, almost all of the clinicians involved in his research felt that severe memory loss, disorientation and a decline in mental functions are the most distinctive symptoms of senile dementia. The physicians studied conducted extensive medical, social and behavioral evaluations of 111 elderly volunteers.

As part of their research, Granick and his colleagues also developed a list of 141 medical and psychological factors which can be used to detect senile dementia in its earliest stages. This list included a

few purely medical variables, such as a history of heart problems, which, according to the investigators, might distinguish individuals with moderate to severe forms of dementia from nondemented subjects if vascular dementia is the cause. None of these medical factors were sensitive enough to detect mild forms of dementia. On the other hand, tests which measured aspects of psychological function showed the extensive and seriously deteriorative effects of senile dementia. Combining tests even made it possible to single out patients who were only mildly demented. According to Granick, performance on behavioral or psychological tests would appear to be more useful than the standard medical measures currently used in the diagnosis of senile dementia.

Granick further refined his list of factors and came up with 15 variables --most of which deal with the quality of intellectual function--which together can serve as a basis for the diagnosis of senile dementia. Using a step-by-step process to measure such functions as mental status and memory, Granick accurately classified 93 percent of a smaller group of volunteers in the study as either mildly demented, suffering from moderate to severe dementia, or nondemented. Since there has never been a single reliable and valid test to diagnose senile dementia in its earliest stages, such work by behavioral scientists may someday prove extremely useful to physicians.

Family Studies

In addition to studying the mechanisms and cause(s) of SDAT, research scientists have begun to take a closer look at the families of SDAT victims. Alternately parallelling, inspiring, and building upon the development of family support groups, these studies have uncovered some intriguing findings about how families cope and how to help them cope.

With support from NIMH, Steven Zarit of the University of Southern California will build upon earlier research on strategies for coping. Zarit and his colleagues have found that health professionals can greatly reduce the amount of stress that impedes a caregiver's ability to function by 1) providing information about the disease, 2) offering alternative solutions for day-to-day problems, and 3) providing an atmosphere whereby relatives, friends, or other caregivers can offer much-needed support. According to the investigators, it is important--but rarely the case--that health professionals take the time to answer the many questions relatives will ask about the causes of the illness, medical treatments that may or may not be helpful or harmful, and what the illness will do to the patient's behavior. Such information is critical to developing reasonable solutions to practical problems the patient may have with eating, sleeping, and other routine behaviors. It is also important to offer caregivers individual or family counselling or to provide a structured environment in which they can discuss their experiences and solutions with others in the same situations. In the end, say the investigators, it is the ability of the caregiver to develop and/or maintain good coping skills, and to be able to count on support from family and friends, which will determine his or her ability to continue providing care, regardless of the severity of the

dementia.

At the University of Michigan, Dorothy Coons and her colleagues have obtained private funding from the American Association for Retired Persons to quantify further the experiences of families. The investigators developed and distributed a questionnaire to 510 families of SDAT victims. Of the 75 percent who returned completed questionnaires, most were caring for relatives at home. Of those who had placed a relative in a long-term care institution, most had maintained the patient at home for as long as possible.

In what amounted to a tremendous outpouring of information, the responses told of the frustrations of obtaining a diagnosis, of patients losing jobs and, oftentimes, benefits before a diagnosis was established, of the guilt which tore families apart when certain decisions were made, and of victims as well as caregivers fighting off alcoholism and depression. The investigators also found evidence of a wide variety of successful coping strategies: in some cases, those who responded felt the disease had acted as a catalyst in uniting the family; in other cases, family members became educators and advocates on behalf of patients. Once again, a major area of concern was the need for more information and emotional support from health professionals and others.

There is a serious need for further research on the experiences and needs of families of SDAT patients. As the primary source of care for those who suffer from senile dementia, the family bears most of the economic and emotional burden of the disease which might otherwise fall on social institutions. Moreover, research is needed on the possible contributions of family reactions to the course of the disease in the patient.

CLINICAL RESEARCH

A number of scientists, including clinicians, gerontologists, biochemists, neuropathologists, neurophysiologists, psychologists, mathematicians, and many others, are employing the early findings of biomedical, social, and psychological studies to design clinical research projects--in particular, studies aimed at improving diagnosis, some of which were highlighted above, and studies aimed at improving treatment.

Sleep Studies

At the University of Washington, investigators receiving support from the NIMH, NIA, and the Veterans Administration are attempting to determine if the sleep and wake patterns of older individuals can be used to detect the presence and monitor the progress of SDAT. In a series of sleep laboratory experiments, Patricia Prinz and her colleagues have looked at healthy young and old subjects and at patients with a diagnosis of SDAT. Her findings in older healthy adults confirm early work on "normal" sleep patterns in the elderly: older people experience less of certain "stages"

of sleep and awaken more frequently throughout the night than healthy young adults. She also found, however, that these and other changes were significantly more pronounced in SDAT patients, including frequent awakenings. The more advanced the disease, the more severe the changes.

In her most recent studies, Prinz finds that impaired sleep is evident even in the very early stages of SDAT and that the changes which occur are striking enough to differentiate healthy subjects from patients with severe, moderate, or even mild cases of SDAT. In the next part of her investigation, Prinz will examine the sleep/wake patterns of elderly individuals who have complaints of memory loss to see if she has indeed found a "marker" to detect early cases of SDAT.

Treatment Approaches

As noted above, one of the most consistent changes in SDAT involves a decrease in the activity of the chemicals collectively comprising the brain's cholinergic system. While recognizing that SDAT probably involves more than one neurotransmitter, basic scientists have attempted to determine what causes this particular decline and clinical scientists have attempted to compensate for this deficit as a way of treating the serious symptoms of SDAT.

The first studies in this area involved ingestion of the drug choline chloride, which not only produced some rather unpleasant side effects, but failed to increase acetylcholine production in the brain. Other early studies employed pure forms of lecithin, the dietary source of choline with the same intent of increasing acetylcholine production. Lecithin increased the level of choline in the blood more than choline chloride, continued to have this effect for a longer period of time, and had no serious side effects--but also showed no consistent or marked benefit.

In 1978, research at the Bronx VA Hospital suggested that physostigmine, a drug which blocks the otherwise fast breakdown of acetylcholine in the brain, had a positive effect on the memory of elderly Alzheimer patients, but that the dose required to do so varied from subject to subject. Use of the drug, however, was plagued by problems. It was hardly practical for SDAT patients since it had to be given by injection and its effects lasted less than one hour. Now, a research team supported by the NIA and the NINCDS at the Albert Einstein College of Medicine may have overcome some of the difficulties inherent in the use of this drug. Using an oral form of physostigmine, Leon Thal found marked improvement in 6 out of 8 Alzheimer patients when the drug dose was carefully planned for each individual and given in combination with lecithin. The drug's effect lasted longer than the investigators anticipated so that memory improvement was still noticeable on the morning after the drug was administered. Also, side effects such as nausea and cramps were only apparent when the patient received more than the optimal dose to improve his/her memory. With support from the NIA, Thal hopes to expand these studies and to begin work on tetrahydroaminoacridine, a drug which also acts to slow breakdown of acetylcholine but may be safer and more effective than physostigmine.

INTRAMURAL INITIATIVES

The NIA Laboratory of Neurosciences (LNS) clinical program, established in 1980, is involved in an intensive investigation of brain metabolism in relation to normal human aging and dementia. In September 1982, Stanley I. Rapoport, LNS chief, and Neal R. Cutler, chief of the LNS clinical program, together with a staff of research neurologists, psychologists, and other health professionals admitted the program's first inpatients thus initiating a series of activities focusing primarily on the dementias and related neuropathological diseases of the elderly. Studies look closely at senile dementia of the Alzheimer's type and at multi-infarct dementia, which is caused by a series of minor strokes.

These studies of dementia are set in the context of a clinical program which has been examining, and which will continue to examine, the normal aging process from biochemical, cardiovascular, and general physiologic perspectives, including careful evaluation of brain function. The primary clinical goals of the new program will be to 1) develop a clearer picture of brain physiology in normal aging and age-related disease; 2) to evaluate the changing pharmacokinetics and pharmacodynamics of various anti-hypertensive and central nervous system agents in the elderly; 3) to develop a better understanding of the causes, courses, and treatments of different forms of dementia; and 4) to encourage other NIH components to focus their clinical studies on the growing aging population.

Rapoport and his staff hope to use the results of their work to eventually design pharmacological approaches to treat reversible cognitive defects of aging and irreversible dementia and to understand better the neurochemical changes that occur in Alzheimer's type dementia.

The principal research efforts of Thomas N. Chase and the NINCDS intramural staff are directed towards the rational development of improved drug treatments for nervous system disease. Of particular interest are the investigators attempts, using human subjects as well as animal models, to relate the activity of particular neurotransmitter systems such as the dopamine system, to specific brain functions. New drugs are then evaluated in animal models and in man for their ability to selectively modify these systems and thus ameliorate debilitating neurologic or psychiatric changes.

This work is being done in addition to PET studies of regional brain activity in Alzheimer's patients, which was outlined above.

In one of several studies on senile dementia, NIMH scientists are continuing their investigations of neurofibrillary tangles in Alzheimer's type dementia. For some time, it has intrigued these investigators that nerve cells with neurofibrillary degeneration may be functionally impaired, but do not seem to rapidly deteriorate and die. If aluminum is, in fact, responsible for some of the degenerative brain changes in Alzheimer's type dementia, then attempts to remove this metal from the human body could have significant effects on the course of the illness. Following the lead of Czechoslovakian investigators who have suggested that aluminum interacts with fluoride ions and

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is in this way excreted from the body, scientists at the NIMH Adult Psychiatry Branch are now conducting a long-term study of the effects of sodium fluoride on the course and outcome of Alzheimer's disease and SDAT. Results in the first patients studied are sufficiently encouraging to warrant continuation of this project. David Shore and Richard Wyatt expect to complete this pilot study during the fall of 1984.

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APPENDIX: TOTAL OBLIGATIONS FOR SDAT AND RELATED DISORDERS
(Dollars in Thousands)

Institute	1976	1977	1978	1979	1980	1981	1982	1983 (est.)
NIA	857	1500	1960	4142	4211	5196	8054	9255
NIMH[1]	728	815	790	1315	2151	4700	4800	4950
NINCDS	2314	2333	2422	2844	4960	5427	6243	6700
NIAID	--	--	--	1381	1775	1394	1256	1435
TOTAL	3899	4648	5172	9682	13097	16717	20353	22340

[1]NIMH is a unit of the Alcohol, Drug Abuse and Mental Health Administration.

Support by the

National Institute on Aging, NIH

of

Research and Research Training Related to
Senile Dementia of the Alzheimer's Type

(Extramural and Intramural Programs)

By Grant/Project Number
Principal Investigator
Institution
Title
Description
Amount of Current Award

As of: February 23, 1983
Prepared for: HHS Secretary's
Task Force on Alzheimer's Disease

Grant Number	Principal Investigator/Institution Project Title/Description	Amount of Current Award (including Indirect Costs)
NIA/EDB/INTRAMURAL Research Contract/Interagency Agreement		
NO1 AG-12106	Evans, Dennis A., M.D. Peter Bent Brigham Hospital Senile Dementia: Natural History The objective of this contract is to identify at least 100 persons afflicted with senile dementia among approximately 3500 noninstitutionalized elderly persons, re-examine them (and controls) at regular intervals over approximately three years in order to develop a better understanding of the usual course of decline (intellectual functioning, independence, illness, death) occurring in such persons. The bulk of the studied persons will not previously have been recognized as demented and will be at an early phase in their illnesses.	$399,912
Y02 AG-20040	Leaverton, Paul, Ph.D. National Heart, Lung, and Blood Institute Investigate Senile Dementia in Framingham Heart Study The major objective of this interagency agreement is to identify factors associated with senile dementia of the Alzheimer's type (SDAT) and multi-infarct dementia (MID) utilizing data collected prospectively over the past 30 years as part of the Framingham Heart Study. Cases of SDAT and MID are currently being identified from among surviving study participants. The information will also be used to estimate prevalence, incidence, diagnostic accuracy, and course of the illness.	80,000
Y01 AG-90020	Locke, Ben National Institute of Mental Health (NIMH) Catchment Area Study of Senile Dementia The Division of Biometry and Epidemiology, NIMH, investigated the prevelance of mental illness in an adult catchment population, Epidemiology Catchment Area Study (ECA). An award was made to Yale University to survey a sample of the New Hampshire, Connecticut, population for this purpose. NIA is specifically interested in defining the prevelance of Senile Dementia in persons over 65 years of age.	No new funding for FY 83 (total thru FY 79-80 $ 835,000)

NIA Intramural Research Program

	Principal Investigator/Institution Project Title/Description	Amount of Current Award (including Indirect Costs)
NIA/INTRAMURAL/LABORATORY OF NEUROSCIENCES (LNS)		
Principal Investigator:	Stanley I. Rapoport, M.D. Chief, LNS National Institute on Aging	$ 2,648,000 4/

Brain Function in Aging and Dementia

Using positron emission tomography, together with 18F-2-deoxy-D-glucose, the investigator is examining overall and regional rates of cerebral glucose utilization in man in relation to age and in Alzheimer's disease.

Characterizing and Diagnosing Alzheimer's Disease

Alzheimer's disease constitutes about 50% of the dementias of old age. Twenty percent are treatable dementias, the remainder are due to vascular insufficiency. The aim of the clinical program, both inpatient and outpatient, is to develop procedures to separate and identify the treatable and non-treatable dementias.

Blood-Brain Barrier Function

The blood-brain barrier at cerebral capillaries regulates drug entry into the brain, brain metabolism and homeostasis, and overall brain function. The aim of this project is to characterize the blood-brain barrier in animals and man, and to determine the extent to which the barrier is altered in dementias such as Alzheimer's disease, and the contribution of such alterations to the disease process.

4/1983 estimate based on the FY 83 Continuing Resolution for the Laboratory of Neurosciences

Principal Investigator/Institution Project Title/Description	Amount of Current Award (including Indirect Costs)

NIA/INTRAMURAL/LABORATORY OF NEUROSCIENCES (LNS)

Development of New CT Techniques for Evaluating and Diagnosing SDAT
The focus of this study is to develop computer assisted tomography (CT) techniques for the evaluation of brain changes in aging and dementia, and for assisting in the differential diagnosis of Alzheimer's disease. New image processing procedures are applied for this purpose to transmit x-ray images of the brain.

Lipid and Protein Biochemistry of the Brain
This project is devoted to develop animal models of aging and disease processes, and understanding of the biochemical regulatory factors relating to neurotransmission and cell maintenance, and those factors which lead to or accelerate brain cell death.

Biological Markers of Alzheimer's Disease
Cerebrospinal fluid and blood for specific chemical or protein changes that characterize Alzheimer's disease as compared to healthy aging control subjects are being investigated.

Down Syndrome-Biochemical Defect in Relation to Dementia and Disturbed Brain Function
Using positron emission tomography to scan the brains of older, demented Down's victims (50+), NIA scientists are studying what appears to be normal levels of glucose metabolism. This finding differs considerably from findings of severely depressed glucose metabolism in Alzheimer brains. However, in Down's patients, markedly elevated levels of glucose metabolism have been found. Over time, then, there appears to be a dramatic drop in glucose metabolism in the Down's brain, just as there is in cases of Alzheimer's disease.

NIA Extramural Grant Program

Grant Number	Principal Investigator/Institution Project Title/Description	Amount of Current Award (including Indirect Costs)
P/B/S: BRCM/MCBB/GEN		
R01 AG-02066-03	Sanders, Marilyn M. Rutgers Medical School	$91,295
	Gene Control & Cyclic Guanosine Monophosphate (cGMP) in Drosophila & Senile Dementia 1/ The objective of this study is to understand the regulation of gene expression, particularly in aging and in age-related dementias. It is postulated that cGMP may play a role in regulation of gene expression during reaction of the cell to environmental stresses.	
R01 AG-02114-03	Shapiro, Burton L. University of Minnesota	72,552
	Cystic Fibrosis and Fibroblasts: Intracellular Calcium 1/ The relationahip between intracellular calcium and senescence in fibroblasts is being studied. Experiments thus far have shown intracellular calcium significantly greater in Cystic Fibrosis than in age, sex, and passage matched control cell cultures. There is considerable evidence that intracellular calcium regulation may play a key role in Alzheimer's disease. This project provides a basic model system to study this crucial process. It is possible that age-related decrement in calcium regulation may be a generalized process present in all types of cells.	
P/B/S: BRCM/PAB/END		
R01 AG-00345-03	Kalu, Dike N. University of Texas	34,238
	Aging and Calcium Metabolism Control 1/ This project is devoted to evaluating age-related changes in hormonal regulation of plasma calcium concentration and skeletal metabolism. Progress to date shows that the hypercalcemic effect of parathyroid hormone in parathyroidectomized prestarved rats is age dependent. The oldest rats studied are still much less sensitive than younger animals, indicating that factors other than calcitonin might be responsible for the age related decrease in the hypercalcemic action of parathyroid hormone. This project also relates to calcium regulation which may play a key role in the etiology of Alzheimer's disease.	

1/Basic
2/Clinical

Grant Number	Principal Investigator/Institution Project Title/Description	Amount of Current Award (including Indirect Costs)
P/B/S: BRCN/PAB/END		
R01 AG-02281-03	Howard, Charles F., Jr. Medical Research Foundation of Oregon	$72,300
	Age-Dependent Changes in Glucose Tolerance Age dependent impaired glucose tolerance in an animal model of human maturity onset diabetes is the primary focus of this investigation. An impairment in glucose tolerance in aging macaca nigra follows a lesion in the islets of Langerhans that is characterized by appearance of amyloid and changes in secretory cell structure and function. The same process might be involved in Alzheimer's disease amyloid formation. There is recent evidence indicating that there is an impairment of brain glucose utilization in Alzheimer's disease. Such a defect may account for the absence of neurochemical defects.	
R01 AG-02599-02	Floyd, Robert A. Oklahoma Medical Research Foundation	63,302
	Neurotransmitters and Oxidative Damage in Aging Brain 1/ Free-radical membrane oxidation in the aging brain and the mechanism by which the neurotoxin 6-hydroxydopamine selectively destroys catecholamine neurons via free-radical intermediates and lipid membrane oxidation are being investigated in this study.	
R01 AG-02778-01	Zbuzek, Vlasta K. University of Medicine & Dentistry of New Jersey	105,551
	Vasopressin (VP) and Aging 1/ It has been shown that the neurohormone VP, in addition to its renal and circulatory actions, improves learning and memory consolidation, increases catecholamine metabolism in the brain and is even considered to be a neurotransmitter.	

Grant Number	Principal Investigator/Institution Project Title/Description	Amount of Current Award (including Indirect Costs)
P/B/S: BRCH/PAB/SEN		
F32 AG-05183-03	Kimes, Alane S. Baltimore City Hospitals	$16,236
	Kinetic Studies of the Blood Brain Barrier 1/ The kinetics of lipid uptake and regional distribution in the brain are being investigated, with the ultimate objective of revealing aspects of fatty acid metabolism related to brain glucose utilization in normal development and aging and in various environmental conditions.	
F32 AG-05183-03S1	Kimes, Alane S. Baltimore City Hospitals	1,255
	Kinetic Studies of the Blood Brain Barrier 1/ This is a supplement related to the above project.	
F32 AG-05268-02	Kosik, Kenneth S. Mclean Hospital Division of Mass. General	20,892
	Cholinergic Activity and Axoplasmic Transport 1/ This research project concerns the relationship between perikaryal neurofibrillary accumulation and diminished choline acetyltransferase (CHAT) activity using aluminum-induced neurofibrillary degeneration as a model for Alzheimer's disease.	

Grant Number	Principal Investigator/Institution Project Title/Description	Amount of Current Award (including Indirect Costs)
P/B/S: BRCM/PAB/SEN		
K04 AG-00028-05	Yen, Shu-Hui C. Yeshiva University The Aging Brain: Immunohistology and Biochemistry 2/ This Research Career Development Award provides for structure-function studies of the immunochemistry and biochemistry of the aging human brain. More specifically, the investigator will focus on age-related changes in the filamentous proteins of the brain, comparing normal brain with those with Senile Dementia of the Alzheimer's Type.	40,338
K04 AG-00084-03	Marotta, Charles A. Mclean Hospital Division of Mass. General Age-Related Changes in Central Nervous System Fibrous Proteins and Messenger Ribio Nucleic Acid 2/ The objective is to study neurofilament proteins and microtubule subunits and to investigate age-related alterations in these proteins	38,718
K04 AG-00085-03	Katz, Ira R. Yeshiva University Hypoxia and Neurotransmitters: Relevance to Aging 2/ Neurochemical effects of cerebral hypoxia are being studied. Progress thus far shows that serotonin formation becomes more sensitive to changes in oxygen availability with decreased tryptophan; in hypoxia, serotonin formation becomes more sensitive to changes in tryptophan availability. These results suggest that each of the oxygenases of catecholamine and serotonin metabolism can become oxygen limited in the range of oxygen tensions that may occur in brain, normally or under pathological conditions.	40,176

Grant Number	Principal Investigator/Institution Project Title/Description	Amount of Current Award (including Indirect Costs)
P/B/S: BRCM/PAB/SEN		
K08 AG-00065-03	Oleshansky, Marvin A. New York University	$48,341
	Serum Dopamine Beta Hydroxylase (DBH) and Organic Brain Syndromes of the Elderly 2/ To determine the relationship between autonomic nervous system function and cognitive impairments in elderly patients with primary degenerative dementia (Senile Dementia of the Alzheimer's Type). The finding of altered serum DBH in patients with primary degenerative dementia would be of diagnostic and theraputic value and would contribute to the knowledge base in this area of research.	
K08 AG-00152-02	Direnfeld, Lorne K. Boston University	46,045
	Parkinson's Disease and Dementia 2/ This project focuses on cognitive dysfunction in Parkinson's disease (PD) with neuropsychological and neurochemical techniques. The first step consists of detailed history and physical-neurological examination, including a mental status examination. The second, a neuropsychological test battery to determine whether dementia exists in all or a subgroup of the initial months of this research project have been spent in the neuropsychological test battery.	

Grant Number	Principal Investigator/Institution Project Title/Description	Amount of Current Award (including Indirect Costs)
P/B/S: BRCM/PAB/SEN		
P01 AG-00795-05	Lasek, Raymond J. Case Western Reserve University Aging Changes in Neuronal Structure and Function 1/ The overall goal of this program project is to identify the cellular and biochemical mechanisms that give rise to age related changes in neurons and that predispose the nervous system to age-related pathologic conditions.	$ 482,070
P01 AG-00905-05	Fox, Jacob H. Rush University Cerebral Decline in Aging 2/ This program project is concerned with investigating changes in cerebral function in aging using both animal and human subjects. The issue of normal versus pathologic cerebral changes with aging are being particularly explored. Longitudinal studies will demonstrate ongoing changes and point out important prognostic predictors.	162,335

Grant Number	Principal Investigator/Institution Project Title/Description	Amount of Current Award (including Indirect Costs)
P/B/S: BRCM/PAB/SEN		
P01 AG-02126-03	Marotta, Charles A. Mclean Hospital Div. of Mass. General Program Project: Molecular Biology of Neuronal Aging 1/ This program project consists of collaborative studies on molecular aspects of the normal and pathological brain aging, focused on neuronal fibrous protein structures: neurofilaments and microtubules. Particular attention will be given to molecular abnormalities seen in Alzheimer disease post mortem brain tissue.	217,721
P01 AG-02132-03	Prusiner, Stanley B. University of California San Francisco Viral Degenerative and Dementing Diseases in Aging 2/ This study focuses on the dramatic degeneration of the central nervous system produced by Scrapie and Creutzfeldt Jakob disease (CDJ) slow transmissible agents which makes these disorders excellent models for studying degenerative diseases whose occurence increases with aging.	212,039
P01 AG-02219-03	Davis, Kenneth L. Mount Sinai School of Medicine Cholinergic Treatment of Memory Deficits in the Aged 2/ Neurochemical and pharmacological studies establish a rationale for clinical trials of drugs that increase central cholinergic activity in patients with a diagnosis of Alzheimer's disease, and in normal elderly people with an age-related loss in memory functioning. The major goal of the project is to test potential cholinomimetic compounds in patients with Alzheimer's disease, normal elderly people with an age-related memory loss and in normal young subjects, to determine the ability of these drugs to enhance memory functioning.	220,672

Grant Number	Principal Investigator/Institution Project Title/Description	Amount of Current Award (including Indirect Costs)
P/B/S: BRCM/PAB/SEN		
P01 AG-02478-03	Katzman, Robert Yeshiva University	$806,708
	Senile Dementia: Alzheimer and Vascular 2/ This program project is concerned with dementias of both the vascular and Alzheimer's type, including laboratory studies to understand the etiology and pathogenesis of Alzheimer's disease (AD), senile dementia of the Alzheimer's type (SDAT), multi-infarct dementia (MID), and volunteer patient studies at the Jewish Home and Hospital for Aged in Manhatten.	
P01 AG-03106-01A1	Manuelidis, Elias E. Yale University	349,478
	Animal Models for the Study of Dementias and Aging 2/ Dr. E. Manuelidis and co-workers, who have pioneered in the development of animal models of human slow viral diseases, propose to refine their understanding about the transmission, clinical variants, course of infection, drug sensitivity and nucleic acid composition of the Creutzfeldt-Jakob Disease agent.	
P01 AG-03272-01	Finch, Caleb E. University of Southern California	256,458
	Aging and Dopaminergic Regulation 1/ The development of anti-idiotype antibodies led to this proposal which consists of three components: neurochemistry, neuropharmacology, and immunology. The focus is on the characteristics of central nervous system dopaminergic systems in the aged mouse, and on the identification of changes which occur in middle life of the animals and which proceed to the aged characteristics that have been, or will be identified.	

Grant Number	Princ'pal Investigator/Institution Project Title/Description	Amount of Current Award (including Indirect Costs)
P/B/S: BRCM/PAB/SEN		
R01 AG-00517-06	Sylvia, Avis L. Duke University	$ 115,796

Brain Function and Oxidative Metabolism During Aging 1/
The objective is to correlate the process of aging with central nervous system homeostatic malfunction. The relationship between cerebral function and age-related changes in tissue bioenergetics and oxidative metabolism was studied with accompanying cerebrovascular alterations in response to: changes in oxygen sufficiency (hypoxia, hyperoxia, and ischemia), and alterations in Central Nervous System (CNS) substrate delivery (hypo-and hyperglycemia); so far on baseline data on mitochondrial redox states in cerebral tissue during "resting" conditions has shown that redox levels of respiratory chain components were altered by changes in oxygen availability, by lung pathology, the relationship between microcirculation and the terminal oxidase step of the respiratory chain.

R01 AG-00847-04	Sladek, John R., Jr. University of Rochester	116,965

Aging: Effects on Peptidergic and Aminergic Neurons 1/
The objectives of this research are to assess age-related changes in central aminergic and peptidergic neurons. To date, perikaryal histofludrescence for all brainstem Dopamine neuron groups examined revealed an age-related decrease in neurotransmitter content. This may be related to decreased transmitter synthesis or to increased neuronal activity with transmitter release exceeding its replacement.

Grant Number	Principal Investigator/Institution Project Title/Description	Amount of Current Award (including Indirect Costs)
P/B/S: BRCM/PAB/SEN		
R01 AG-01066-03	Davies, Peter Yeshiva University	$117,279
	Aging & Dementia: Cholinergic Neuron Biochemistry 1/ In studying the decline of enzyme activity in central cholinergic neurons in normal aged persons and in persons with Alzheimer's type dementia, data from 50 brains of Alzheimer's disease/Senile dementia of the Alzheimer's Type (AD/SDAT) cases have confirmed a reduction in Choline Acetyltransferase (CHAT) activity and the presence of neuritic plaques and neurofibrillary tangles in AD/SDAT. Results indicated that while a low CHAT activity is sufficient to produce dementia, it is not the only deficiency that can produce this condition. The literature indicates that in normal elderly persons there is an age related loss of CHAT activity, but five persons (aged 90 or older at time of death) represented in this study who scored well in psychometric and clinical test batteries did not exhibit this age related loss of CHAT activity.	
R01 AG-01066-03S1	Davies, Peter This is a supplement which relates to the above project.	115,095
R01 AG-01121-05	Coleman, Paul D. University of Rochester	63,361
	Computer Aided Study of Dendrites in Aging Human Brain 1/ Samples of parahippocampal gyrus (entorhinal cortex) were taken from human brains at autopsy and stained by the Golgi Cox method to reveal the dendrites of individual nerve cells. Classification as normal aged or senile demented was based on both behavioral and neuropathological criteria. These data suggest a model in which aging cortex contains both regressing, dying neurons and surviving, growing neurons. In normal aging it is the latter group that predominates up to some undefined age limit. During the coming year these data will be extended to a wider range of ages and to additional brain regions.	

Grant Number	Principal Investigator/Institution Project Title/Description	Amount of Current Award (including Indirect Costs)
P/B/S: BRCM/PAB/SEN		
R01 AG-01136-05	Yen, Shu-Hui C. Yeshiva University	$ 71,300
	The Aging Brain: Immunohistology and Biochemistry 2/ The objective of this proposal is to learn the molecular nature of paired helical filaments (PHF), the main morphological lesion of Alzheimer dementia. Antisera prepared against two cycle purified microtubules of normal human brain was reported to bind to structures resembling the neurofibrillary tangles of Alzheimer dementia.	
R01 AG-01307-03A1	Selkoe, Dennis J. Mclean Hospital Division of Mass. General	161,749
	Aging in the Brain: Role of the Fibrous Proteins 1/ The central objective of this proposal is an improved understanding of the macromolecular pathology of age-related neuronal attrition in the human brain--to understand the role of the neuronal fibrous proteins, in particular, and other structural proteins in the normal age-related atrophy of neurons and in the pathogenesis of presenile and senile dementia of the Alzheimer type.	
R01 AG-01415-04	Perl, Daniel P. University of Vermont & State Agricultural College	125,866
	Trace Elements in Aged Neurons and Senile Dementia 2/ In investigating the role of trace elements in senile dementia of the Alzheimer's type (SDAT), aluminum accumulations (AL) have been noted in 90% of neurofibrillary tangle (NFT), bearing hippocampal neurons of three SDAT patients. Adjacent non-NFT neurons were free of detectable AL. Neurons of non-demented elderly controls were free of AL, except for occasional NFT bearing neurons (89% positive).	

Grant Number	Principal Investigator/Institution Project Title/Description	Amount of Current Award (including Indirect Costs)
P/B/S: BRCM/PAB/SEN		
R01 AG-01529-04	Schuman, Leonard M. University of Minnesota	$ 52,200
	Epidemiologic Study of Alzheimer's Disease 2/ The primary objective is to explore by a case-control study factors of possible etiologic significance to the occurrence of Alzheimer's disease. Variables relevant to viral, genetic and immunological hypotheses are being studied and data on occupational and environmental exposures, drug use, psychological stress, smoking and alcohol consumption will be collected.	
R01 AG-01552-03	Landfield, Philip W. Wake Forest University	61,024
	Hormonal-Pharmacological Studies of Brain Aging 1/ This project is aimed at systematic long-term studies analyzing the effects of hormonal and pharmacological agents on brain aging. Aging rats (17-27 months) that were adrenalectomized and maintained on very low glucocorticoid supplements exhibited fewer morphological signs of brain aging than age matched controls i.e., less marked decrease in neuronal density, fewer reactive glial changes).	
R01 AG-01552-03S1	Landfield, Philip W. This is a supplement which relates to the above project.	16,629

Grant Number	Principal Investigator/Institution Project Title/Description	Amount of Current Award (including Indirect Costs)
P/B/S: BRCM/PAB/SEN		
R01 AG-01572-04	Smith, Dean O. University of Wisconsin	63,855
	Synaptic Structure and Function During Senescence 1/ This investigation is aimed at determining the mechanisms that underlie the deterioration of synaptic function during senescence. The postsynaptic response to acetycholine (ACH) will be examined by applying ACH iontophoretically, and measuring functional sensitivity, desensitization, supersensitivity, and membrane conductance.	
R01 AG-01737-04	Landfield, Philip W. Wake Forest University	49,244
	Neurophysiological Studies of Brain Aging 1/ Correlating age-related changes in hippocampal neurophysiology with memory deficits is the objective of this study. The occurrence of a specific synaptic deficit, frequency potentiation in the hippocampus, has been shown to be very highly correlated with a behavioral retention performance deficit found in old rats. The specificity of the deficit indicates that there is not simply a generalized breakdown in brain function with age. Studies to develop a reliable morphologic correlate of brain aging have led to the quantification of a morphologic change.	

Grant Number	Principal Investigator/Institution Project Title/Description	Amount of Current Award (including Indirect Costs)
P/B/S: BRCM/PAB/SEN		
R01 AG-01896-03	McClure, William O. University of Southern California	$ 75,894
	Neuroleptics, Aging, and Cholinergic Function 1/ The objectives are to examine the age-related changes in the molecular regulation of the enzyme choline acetyltransferase (CAT) and to measure the effect of neuroleptic drugs on these changes. Attempts to raise monoclonal antibodies to CAT by injecting mice with rat CAT are progressing, and assays of these antibodies are underway. The investigators are searching for alternative models since studies to detect age-related decreases in CAT in rats and mice have been unsatisfactory because old rats and mice have levels of CAT comparable to young adult controls.	
R01 AG-01973-03	Gorevic, Peter D. State University New York Stony Brook	38,233
	Senile Amyloidosis: Biochemistry & Immunohistochemistry 2/ The investigators are delineating the biochemical and immunohistochemical properties of amyloid associated with aging in man. They have already found that amyloid fibrils were demonstrated in top-layer preparations after water extraction. The major subunit protein of these preparations was a 14,000 dalton molecule with amino acid composition resembling that of plasma prealbumin.	
R01 AG-02496-02	Rapport, Maurice M. New York State Psychiatric Institute	85,375
	Membrane Pathology in Aging and Senile Dementia 2/ Morphological evidence indicates that aging in the brain is associated with regression in dendrites of some cells and growth in dendrites of others, whereas in senile dementia only regression is observed. Biochemical measurements of sialic acid content tend to confirm the loss of axodendritic processes in showing a 20% greater loss in senile dementia than in aging. This project will develop additional biochemical criteria to establish whether membrane pathology is involved in aging and in senile dementia.	

Grant Number	Principal Investigator/Institution Project Title/Description	Amount of Current Award (including Indirect Costs)
P/B/S: BRCM/PAB/SEN		
R01 AG-02650-03	Johnson, Anne B. Yeshiva University Pathogenesis of Senile Dementia & Cerebral Aging 2/ This research aims to increase understanding of the pathogenesis of Alzheimer's disease and senile dementia of the Alzheimer type (SDAT) by investigating the composition and characteristics of the neurofibrillary tangles (NFT) and neuritic, or senile, plaques which are central features of the pathology of SDAT. The overall objective is to elucidate changes and disease processes in SDAT and to seek clues to its etiology.	$ 77,762
R01 AG-02680-02	Buell, Stephen J. University of Rochester Quantitative Study of Dendrites in Aging and Dementia 2/ This proposal is an extension of ongoing work in our laboratories involving the computer-assisted collection and analysis of quantitative data from Golgi-type preparations of normal aged and demented human brain.	81,660
R01 AG-03047-02	Ball, Melvyn J. University of Western Ontario Clinical and Pathological Study of Alzheimer's Disease 2/ One hundred and fifty organically demented patients are being investigated by standardized neurological and psychiatric examination; specialized psychometric instruments; quantitative 16-channel electroencephalography (with pattern visual evoked response); and quantitative computerized tomographic radiography (including hippoampal thin slices). Patients will be grouped clinically into Alzheimer's Disease; Multi-infarct dementia; Mixed; and Other.	252,911

Grant Number	Principal Investigator/Institution Project Title/Description	Amount of Current Award (including Indirect Costs)
P/B/S: BRCM/PAB/SEN		
R01 AG-03359-01	Price, Donald L. Johns Hopkins University	$159,654
	Alzheimer's Disease: Nucleus Basalis/Cholinergic Defect 2/ This study is primarily devoted to testing hypotheses related to recent evidence which suggests that much of the cholinergic cortical innervation arises from the neurons in the nucleus basalis of Meynert (nbM). Preliminary evidence suggests that loss of nbM neurons is a pathological correlate of the deficiency of cholinergic markers in cortex.	
R01 AG-03410-01	Morrell, Frank Rush-Presbyterian-St. Lukes Medical Center	113,055
	Neurobiology of Age-Related Deficit in Memory 1/ The intent of this project is to elucidate some electrophysiologic and biochemical aspects of age-related memory loss in rats. The applicants report that Fischer 344 rats, aged 26 months or older, have difficulty learning to correctly run an eight arm spatial maze, a procedure which apparently cannot be performed by young rats with damage to the hippocampal formation. They reason that the inability of the elderly rats to learn this task indicates the presence of age-related changes in the hippocampus, and have proposed a series of electrohysiological and biochemical studies to further investigate this hypothesis.	
R01 AG-03571-01	Gershon, Samuel Wayne State University	125,001
	Cholinergic and Cerebrovascular Functions in Aging 2/ This study examines the changes in various parameters of brain cholinergic function, cerebrovascular function and behavior during aging in the male Sprague-Dawley rat. An additional goal is to establish the effect that rearing environment has on age-related span changes in cognitive performance, cholinergic functioning and cerebralcirculation.	

Grant Number	Principal Investigator/Institution Project Title/Description	Amount of Current Award (including Indirect Costs)
P/B/S: BRCM/PAB/SEN		
R01 AG-03932-01	Weiner, Norman University of Colorado Health Sciences Center	$ 99,519
	Brain Mondamines, Protein Phosphorylation, and Aging 1/ It is well known that a variety of enzymes and receptors involved in neurotransmitter function decrease in activity with the age of the organism. This project is designed to examine factors involved in catecholamine synthesis and release in order to determine which systems are most affected during aging.	
R01 AG-04171-03	Gibson, Gary E. Burke Rehabilitation Center	96,634
	Neurotransmitter & Energy Metabolism 1/ In order to test the hypothesis that neurotransmitter synthesis in the brains of aged animals is even more sensitive to hypoxia than in the brains of younger animals, the synthesis of acetylcholine and other neurotransmitters derived from glucose (glutamate, aspartate, and gamma-aminobutyrate) will be studied with varying levels of chemical and hypoxic hypoxia in the brains of young, mature and aged mice and rats. The synthesis of acetylcholine and the other neurotransmitters will be studied with (U-14C) glucose by methods developed by the Principal Investigator.	
R03 AG-03605-01	Galardy, Richard E. University of Kentucky	20,372
	Choline Acetyltransferase in Alzheimer's Disease 2/ This proposal aims to test whether chronic inhibition of brain choline acetyltransferase in rabbits will produce the plaques and neurofibrillary tangles associated with the disease in humans. Autopsied brain tissue from patients with the disease shows levels of choline acetyltransferase and acetylcholinesterase reduced to 10 to 30% of that of age-matched controls. Levels of several other neurotransmitters and enzymes are normal, suggesting a selective degeneration of cholinergic neurons and therefore a specific mechanism for Alzheimer's disease.	

Grant Number	Principal Investigator/Institution Project Title/Description	Amount of Current Award (including Indirect Costs)
P/B/S: BRCM/PAB/SEN		
R01 AG-03674-01	Ochillo, Richard F. Xavier University of Louisiana	$ 19,985
	Cholinergic Muscarinic Receptor and Aging 2/ This proposal deals with a potentially important area of research; namely, age-related changes in muscarinic receptor activity. The investigator proposes to determine whether there are aged-related changes in sensitivity of muscarinic receptors in the ileum of mice, rats and guinea pigs.	
R03 AG-03701-01	Nemeroff, Charles B. University of North Carolina Chapel Hill	18,862
	Neuropeptides in Senile Dementia of the Alzheimer Type 2/ The etiology and pathogenesis of Alzheimer's Disease is poorly understood. Effective treatment for this disease is unavailable. This study focuses on specific central nervous system neurotransmitter circuits in Senile Dementia of the Alzheimer's type.	
R03 AG-03717-01	Dray, Andre University of Arizona	15,570
	Adrenergic-Cholinergic Actions Related to Dementia 2/ This study is associated with the fact that loses of noradrenergic and cholinergic markers from a number of brain region, particularly the cerebral cortex have been recognized in Senile Dementia of the Alzheimer's Type. The investigation is aimed at an understanding of whether the function of the substantia innominata (SI) is regulated by noradrenergic projections and whether these projections also influence target cells of the SI in the cerebral cortex.	

Grant Number	Principal Investigator/Institution Project Title/Description	Amount of Current Award (including Indirect Costs)
P/B/S: BRCM/PAB/SEN		
R03 AG-03720-01	Lenox, Robert H. University of Vermont & State Agricultural College	$ 21,446
	Muscarinic Receptor Subtypes: Tools for Aging Research 1/ This proposal initiates an investigation to characterize a broad spectrum of cholinergic antagonists for their abilities to differentiate muscarinic receptor subtypes. Once this has been accomplished, these antagonists will be utilized in a neurally derived intact cell system which is known to possess muscarinic receptors and responses, to determine which muscarinic receptor subtype(s) is coupled to the adenylate cyclase response.	
R03 AG-03736-01	Crews, Fulton T. University of Florida	20,476
	Age Dependent Changes in Synaptosomal Membrane Fluidity 1/ The specific aim of this proposal is to purify the synaptosomal plasma membrane (SPM) from rats of various ages and to determine if there are changes in the lipid composition and/or fluidity of this neuronal plasma membrane during aging.	
R13 AG-03540-01	Watson, James D. Cold Spring Harbor Laboratory	30,672
	Conference on Biological Aspects of Alzheimer's Disease 2/ This interdisciplinary conference will cover several evolving approaches to understanding the etiology and pathogenesis of Alzheimer's disease.	

Grant Number	Principal Investigator/Institution Project Title/Description	Amount of Current Award (including Indirect Costs)
P/B/S: BRCM/MCBB/SEN		
R23 AG-01948-03	Michaelis, Mary L. University of Kansas Lawrence	$38,453
	Adenosine as a Metabolic Autoregulator in Aging Brain 1/ The objective of this study is to evaluate the age-related changes in the effects of adenosine and its analogues on synaptic membrane potentials and neurotransmitter release processes. Preliminary data suggest that freshly prepared brain synaptosomes from aged rats are similar to synaptosomes from their younger cohorts in magnitude of calcium uptake and sensitivity to depolarizing stimuli. This study will attempt to illusidate basic membrane process which may account for the neuropathological changes in Senile Dementia of the Alzheimer's Type.	
R23 AG0-3254-01	McNeill, Thomas H. University of Rochester	53,306
	Histochemical Studies of the Aged Basal Ganglia 1/ We propose to examine the morphology and cytoarchitecture of dopamine (DA)-containing nuerons of the stustantia nigra and substance P or Gamma Amino Butyric Acid (GABA) containing nuerons of the striatium and the morphological and synaptic relationship between striatonigral SP or GABA and bugristruatak DA pathways in the aged brain.	
T32 AG-00007-08	Vogel, F. Stephen Duke University	57,124
	Biological Approaches to Dementia 2/ Three postdoctoral trainees are supported each year for multidisciplinary postdoctoral training in dementia. Research projects of current trainees include studies of the cholinergic neurons of the hypothalamus, particularly those to the nucleus basalis of rats.	

Grant Number	Principal Investigator/Institution Project Title/Description	Amount of Current Award (including Indirect Costs)
P/B/S: BROM/MCBB/SEN		
T32 AG-00061-05	Appel, Stanley H. Baylor College of Medicine Biological Approaches to Dementia 2/ This support provides postdoctoral training for 3 trainees in the physiological and morphological approaches to dementia.	$33,850
P/B/S: BHCM/GB/GER		
P01 AG-03934-01	Kaye, Donald Philadelphia Geriatric Center-Friedman Hospital Teaching Nursing Home Award 2/ A subproject of this Teaching Nursing Home Award, Biological Approaches to Dementia, focuses on a straightforward experiment that has been designed to compare intensive cognitive rehabilitation with routine methods of rehabilitation in a large number of stroke patients by specified psychometric, neurological, and behavioral measurement. In addition, the investigators offer objective, independently derived pathophysiological analyses using regional cerebral blood flow measurements in conscious patients.	896,204 3/
P01 AG0-3934-01S1	Kaye, Donald Philadelphis Geriatric Center-Friedman Hospital Teaching Nursing Home Award 2/ This is a supplement which relates to the above program project.	51,686

3/A portion of this award is related to SDAT

Grant Number	Principal Investigator/Institution Project Title/Description	Amount of Current Award (including Indirect Costs)
P/B/S: BRCM/GB/GER		
P01 AG-0-3949-01	Katzman, Robert Yeshiva University	$ 758,978 3/
	Teaching Nursing Home 2/ This Teaching Nursing Home Award includes the three-part subproject on dementia: a) a rational and important therapeutic trial (of physostigmine); b) a rational and important extension of current Albert Einstein studies on the clinical, anatomic chemical and pathological characteristics of Alzheimer's disease and other dementias; and c) a somewhat weaker subproposal on psychiatric disabilities in nursing home patients.	
P01 AG0-3949-01S1	Katzman, Robert Yeshiva University	27,216 3/
	Supplement to TNH Awarded 093082 2/ This is a supplement which relates to the above Teaching Nursing Home Award.	
P/B/S: BRCM/GB/PHR		
R03 AG-03672-01	Tune, Larry E. Johns Hopkins University	20,850
	Neuroleptic Drug Level Monitoring in Dementia Syndromes 2/ The applicant is studying the effects of two neuroleptic drugs on three subtypes of dementia. Results from these studies are meant to provide more knowledge about the effects of commonly used drugs employed in the management of dementia. Recent developments in neurotransmitter and drug binding assays have made it possible to augment clinical knowledge of dementia by means of drug level monitoring techniques which allows one to appreciate drug effects on multiple neurotransmitter receptor systems. The proposed studies represent an attempt to apply these recent advances in neurotransmitter receptor pharmacology and technology to patients with dementia syndromes.	

3/A portion of this award is related to SDAT.

Grant Number	Principal Investigator/Institution Project Title/Description	Amount of Current Award (including Indirect Costs)
P/B/S: BSR/CBA/BPA		
R01 AG-03354-01	Poon, Leonard W. Massachusetts General Hospital Cognitive Deficit Identification in Dementia 2/ The research will examine the differential degree to which deficits in processing capacity and processing speed (timing and activation) contribute to the cognitive dysfunction of three neurologic populations who vary in the distribution of cortical and subcortical pathology, grouped as follows: demented patients with Alzheimer's Disease and with Progressive Supranuclear Palsy, and both demented and non-demented patients with Parkinson's Disease.	$87,959
P/B/S: BSR/CBA/CAG		
P01 AG0-2269-03	Weintraub, Sandra Beth Israel Hospital Reversible Changes of Cognition in the Elderly 2/ The objective of this program project in aging is to establish an integrated program of clinical research in the neurological concomitants of aging and dementia. The project is multi-disciplinary in nature. The goal is to determine the relationship between neuropsychological, neurophysiological and neuroanatomical measures in healthy aging individuals and in patients with Alzheimer's disease.	156,325
R01 AG-00445-08	Smith, Anderson D. Georgia Institute of Technology Interaction Between Human Aging and Memory 1/ This is a proposal to continue an investigation of memory and aging. The past progress has been good and three of the five experiments proposed are expected to yield useful empirical data. Qualitative and quantitative processing differences in memory will be studied.	35,997

Grant Number	Principal Investigator/Institution Project Title/Description	Amount of Current Award (including Indirect Costs)
P/B/S: BSR/CBA/CAG		
R01 AG-02231-04	Schwartz, Myrna F. University of Pennsylvania	$169,175
	Patterns of Cognitive Deficit in Alzheimer's Disease 2/ This proposal deals with patterns of cognitive deterioration in Alzheimer's disease, and irreversible dementing disease associated with diffuse degenerative changes in the gray matter of the brain. It is now recognized that Alzheimer's disease accounts for at least one half the population diagnosed as having senile dementia, and for the majority of dementias arising before senescence.	
R01 AG-02427-02	Camp, Cameron J. Fort Hays State University	14,283
	Aging and Memory: Fact Retrieval Versus Inference 1/ The relationship between aging and the retrieval of information stored in memory will be examined. Previous research has indicated that despite an absence of evidence of memory decrease in the aged in objective measures of performance on memory tasks, the elderly incorporate negative stereotypes about such a decrease into their own self-images.	
R01 AG-02452-03	Light, Leah L. Pitzer College	66,558
	Contextual and Semantic Memory Processing in Old Age 1/ The object of this study is to determine the effect of age-related changes in contextual and semantic information processing on language comprehension and memory. List discrimination data have indicated that overall recognition performance by the old and very old was lower than performance by the young.	

Grant Number	Principal Investigator/Institution Project Title/Description	Amount of Current Award (including Indirect Costs)
P/B/S: BSR/CBA/CAG		
R01 AG-02751-02	Howard, Darlene V. Georgetown University	$ 36,189
	Studies of Aging, Semantic Processing, and Memory 1/ Processes of memory activation that change during aging from those that do not will be differentiated. In the pilot experiment, response times to words were shorter than those to nonwords, response times to words correlated negatively with the frequency of the words in the english language, and response times for both words and non words correlated positively with the number of letters and syllables.	
R01 AG-03051-01	Reisberg, Barry New York University	127,686
	Aging and Dementia: Longitudinal Course of Subgroups 2/ This study will test hypothses related to the prognosis and course of the early stages of cognitive decline associated with senile dementia of the Alzheimer's type for the proper assessment of treatment modalities and for the counseling of patients and their relatives.	
R23 AG-02802-02	Mayeux, Richard P. Columbia University	49,986
	Depression and Parkinson Disease: A Model in Aging 2/ Biologic factors in depression associated with Parkinson's disease will be evaluated and related to a model of the depression that occurs in the aged.	

Dr. RINGLER. Before closing, I would like to highlight a most important aspect of the human tragedy associated with Alzheimer's disease; namely, the need to mobilize support for families of Alzheimer victims. In the fall of 1979, the National Institute on Aging and the National Institute of Neurological and Communicative Disorders and Stroke brought together representatives of seven independent groups to discuss the feasibility of creating a national network for the support of families of Alzheimer victims. As pointed out in Secretary Heckler's statement, an organization called the Alzheimer's Disease and Related Disorders Association came into being during that meeting, and, by January 1983, had formed 66 chapters in 30 States and the District of Columbia. By the end of this year, the organization hopes to have chapters in every State.

In summary, Mr. Chairman, as has been said many times now during this hearing, Alzheimer's disease is most dreaded, both by its victims and their families. There is currently no established treatment and no cure. However, great strides have been made in research during recent years, and we are extremely optimistic for future research in this area.

Thank you.

Senator GRASSLEY. Well, thank you all very much. I want to compliment all of you on the quality of your testimony, but more importantly, on the diligence of your work and those who work under you in trying to find a solution to this disease.

Each of you spoke to a considerable extent about grants that are being used in Alzheimer's research. I believe that our record could potentially benefit from a breakdown of grants that each Institute currently utilizes in research in this area. Could you each supply to the subcommittee in the near future a listing of the grants, so we might ascertain what support is available?

Dr. RINGLER. Yes.

Dr. PARDES. Yes, Senator.

Dr. GOLDSTEIN. Yes.

Senator GRASSLEY. Thank you.

[The prepared statement of Dr. Ringler and material referred to follows:]

STATEMENT BY

ROBERT L. RINGLER, PH.D.
ACTING DIRECTOR, NATIONAL INSTITUTE ON AGING
NATIONAL INSTITUTES OF HEALTH

Thank you for this opportunity to testify, together with my colleagues. I am pleased to present an overview of the National Institute on Aging's programs on senile dementia of the Alzheimer's type (SDAT), and to report on recent progress in research on this disorder.

Since the inception of the National Institute on Aging, the Institute's leadership has concentrated heavily on the positive aspects of aging. With certain broad objectives in mind--such as developing a better understanding of normal aging and promoting health and effective functioning--we have supported studies that contradict pervasive myths and stereotypes associated with aging in America. Our public statements on dementia in the aged have emphasized that only about 5 percent of the 26 million Americans over 65 suffer the cognitive deficits formerly thought to be a normal part of old age.

But a closer inspection of the statistics shows that the problem is far more significant. Between the ages of 60 and 80, the risk of developing dementia doubles every five or six years. Currently, one third of the entire population in developed countries will live to age 80 and beyond when there is an estimated 20 percent chance that a person will have serious, irreversible dementia. There is an assumption that beyond age 80, the risk continues to increase at the same general rate, but the data are scarce among these older populations. The data do show, however, that the over 85 age group is the fastest growing segment of the older population. During the 25 years between 1978 and 2003, it is estimated that the number of persons in the over 85 age group will increase by 84 percent.

Almost since the NIA was established, research on SDAT has been one of the Institute's highest program priorities. The NIA's interest in this area of research is in keeping with the legislative mandate which directs the Institute to foster scientific research not only on the normal aging processes but also on the diseases and other special problems and needs of the aged. Failure in cognitive functioning is one of the principal reasons for institutionalization of the elderly. In 1976, less than one million dollars from the NIA budget was spent on research in this area; in 1983, this figure is expected to exceed eleven million dollars, in part due to increased numbers of research and research training grants related to SDAT, and in part due to the addition of the Institute's Epidemiology, Demography and Biometry Program and an intramural Laboratory of Neurosciences, both of which have active SDAT research projects.

Some of the most significant research accomplishments of recent years are related to the definition and detection of SDAT. Little more than five years ago, all but a handful of experts in the scientific and medical communities believed that Alzheimer's disease was a rare neurological disorder which typically occurred in persons in their late 40's and early 50's. At the same time, it was generally accepted that forgetfulness, confusion and other "senile-like" symptoms were a normal part of aging. In 1977 and 1978, two major international conferences sponsored by the National Institute of Neurological and Communicative Disorders and Stroke, the National Institute on Aging, and the National Institute of Mental Health focused on the pathological and clinical relationship between senile brain disease and Alzheimer's disease. In 1979, an NIH consensus development conference

on treatment possibilities for mental impairment in the elderly helped focus attention on the difference between normal aging and dementia. As a result of these and other efforts, senile dementia of the Alzheimer's type is today recognized as the most common cause of severe intellectual impairment in older individuals. Whether the presenile form of Alzheimer's disease is identical in cause, mechanisms, and course to SDAT is still not completely established. Nonetheless, SDAT is recognized as a pathological condition of the brain and not a condition or a part of normal aging. This is enough to encourage medical science to study the disease and develop a foundation for effective treatment and prevention.

Because of studies during the last decade, considerable information is now available about SDAT and its possible causes. One particularly exciting theory involves destructive changes in brain chemistry. Scientists have consistently associated SDAT with a defect in the availability of acetylcholine, a neurotransmitter involved in both learning and memory. Decreases in the activity of choline acetyltransferase (CAT), a key ingredient in the chemical process which produces acetylcholine, have been linked to changes in cognition and to pathological changes in the brains of SDAT victims. Although SDAT probably involves more than one neurotransmitter, this finding makes it possible to begin to consider treatment strategies. Clinical scientists are attempting to compensate for this defect by replacement therapy or by approaches that would increase synthesis or stimulate more effective utilization of the neurotransmitter in the SDAT brain.

The first studies in this area involved drugs and dietary supplements used to increase the brain's available source of

choline, a precursor of acetylcholine. These studies were largely disappointing. More recent studies are looking at drugs which block the otherwise fast breakdown of acetylcholine in the brain. Studies of the drug, physostigmine, have been particularly exciting to researchers pursuing this approach. Still, the search goes on for a safe drug which can effectively alleviate the most serious symptoms of SDAT. However, I think it is important to emphasize that there is no established treatment that will prevent or reverse what happens to the brain in cases of SDAT.

A second leading theory involves the apparent link between the formation of abnormal proteins in the SDAT brain and the level of certain trace metals inside the brain cells. For some time it has been known that aluminum accumulates in the affected nerve cells of subjects showing the classic neurofibrillary tangles of Alzheimer's disease. Recently, a group of scientists reported high accumulations of aluminum, iron and calcium in the brains of patients who had died of two chronic disorders resembling Alzheimer's disease in its presenile form. The subjects were Chamorro natives of Guam who had amyotrophic lateral sclerosis (ALS) or parkinsonism-dementia. The scientists were NIA-supported investigators at the University of Vermont and researchers from the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS).

Samples of garden soil and drinking water in Guam, as well as in parts of Japan and New Guinea that are similarly plagued by high incidences of ALS and dementia, indicate low levels of calcium and magnesium and unusually high levels of aluminum. All of these

elements are quite similar chemically. Scientists have never been able to demonstrate that aluminum alone predisposes a person to, or causes, SDAT. One potential hypothesis is that high intake of trace aluminum from the soil over a long period of time, coupled with chronic low intake of vital minerals such as calcium and magnesium, ultimately results in a breakdown of the normal mechanisms which metabolize these minerals.

Several Public Health Service (PHS) grantees are currently exploring changes in the cell that might link what appear to be diverse theories on the causes of SDAT. It has been proposed that the abnormal changes in the SDAT brain may be due to the inability of brain cells to regulate calcium levels within the cell. Calcium is a key element in maintaining the excitability of the cell.

Each of these theories on the cause of SDAT is closely linked to questions about brain metabolism. Since 1978, the NIA Laboratory of Neurosciences, under the direction of Dr. Stanley Rapoport, has been involved in an intensive investigation of brain metabolism and normal aging. In 1982, the Institute established a clinical research program at the Warren G. Magnuson Clinical Center at NIH, with use of a six bed patient care unit. In September, the program admitted its first inpatients and initiated a series of activities focusing primarily on SDAT and related neuropathological diseases of the elderly.

Until recently, scientists in the Laboratory of Neurosciences and other laboratories at the National Institutes of Health have focused on cerebral metabolic changes with normal aging. One of the most remarkable finding thus far indicates that there is no

change in the rate of glucose metabolism in the unexcited aging brain. Glucose metabolism is one of three major interconnected measures of brain metabolism--the other two are brain blood flow and brain oxygen consumption. Positron emission tomography (PET), a noninvasive approach which utilizes computer technology, allows simple tests of glucose metabolism and, in turn, provides a direct measure of activity in any given brain region. Rapoport's staff have examined 55 men, aged 21 to 83, and find that the healthy aged brain appears to be as active and efficient as the healthy young brain. They have also looked at a group of 12 Alzheimer patients and have found depressed glucose metabolic rates related to the severity of the disease, in several brain regions.

The NIA investigators studying senile dementia have also made several interesting observations in work with Down's syndrome patients. Previously, PHS-supported genetic studies have noted an increased frequency of Down's syndrome in the families of some Alzheimer patients. Down's patients, who are severely retarded mentally, begin to develop clinical signs of dementia around age 30; at autopsy, there is a marked similarity in the brain pathology of older Down's victims and Alzheimer victims. Using PET to scan the brains of Down's victims aged 50 and over, NIA scientists found what appeared to be normal levels of glucose metabolism. However, when the investigators tested young Down's patients, they found markedly elevated levels of glucose metabolism. Over time, then, there appears to be a dramatic drop in glucose metabolism in the Down's brain, just as there is in cases of Alzheimer's disease.

For the future, NIA hopes to continue to expand research studies

that will lead to improved care and treatment of SDAT victims. The PHS's extramural programs currently support a broad range of research grants dealing with the differential diagnosis of dementia; the pathology of SDAT; the cause(s) of SDAT, including studies of neurochemistry, genetics, immunology, virology, and toxicology; behavioral changes in SDAT; and treatment possibilities. Currently, the NIA also supports a special award, the Teaching Nursing Home Award, which allows investigators to study SDAT and other chronic health problems that are often the cause of institutionalization of the elderly. In this special environment, researchers can study the multiple facets of SDAT that are not normally seen in acute care hospitals.

The NIA Epidemiology, Demography and Biometry Program (EDPB) is moving forward in studies of the incidence, prevalence, natural history, and risk factors of SDAT. In one EDBP project, investigators will observe and describe the course of intellectual decline and general health in a group of SDAT victims and controls. In a second study, researchers are taking a close look at the participants in the Framingham Heart Study who have developed dementia in old age. Volunteers in this study have had 17 comprehensive examinations over a 30 year period. The extensive data on these subjects may help identify important factors associated with the development and course of SDAT. Finally, NIA and NIMH scientists are concluding their study of the prevalence of senile dementia in a New Haven community population of 3,000 persons who are 65 years of age or older. A key element in all of these studies is to observe SDAT patients prior to institutionalization. An important goal is to learn enough

about the disease to develop more sensitive and reliable diagnostic tests.

Future plans for the NIA Laboratory of Neurosciences also include an attempt to characterize the natural course of SDAT, clinically, neuropsychologically and by means of laboratory tests. In addition, investigators in the Laboratory's clinical program will select typical cases for studies of possible therapeutic drugs. During this coming summer, the basic research program of the laboratory will be relocated from the NIA Gerontology Research Center in Baltimore to the Clinical Center at NIH. This move will greatly facilitate NIA's overall research efforts related to the dementias and will make possible cooperative activities with other institutes.

In keeping with its mission related to research on aging and the diseases of aging, in both 1981 and 1983, NIA staff prepared a progress report on SDAT research within the Public Health Service. These reports have been made available to Congress and all other interested parties. The 1983 version discusses in detail some of the cooperative activities among the institutes involved in research on dementia in the aged. These activities include collaboration among intramural scientists, interagency agreements, joint funding of conferences, joint issuance of program announcements, and collaboration on assignment of research grant applications.

Before closing, I would like to add a few words about what I think is the most positive development of recent years--the mobilization of support for families of SDAT victims. In the fall

of 1979, NIA and NINCDS brought together representatives of seven independent groups to discuss the feasibility of creating a national network for the support of families of SDAT victims. An organization called the Alzheimer's Disease and Related Disorders Association (ADRDA) came into being during that meeting and by January 1983 had 66 chapters in 30 States plus the District of Columbia. By the end of this year, the ADRDA hopes to have chapters in every State.

In summary, SDAT is a deadly disease; there is currently no cure. Great strides have been made in research during recent years; I have summarized a few of them earlier in this statement. The brunt of caregiving and mobilizing resources typically falls on the family. As a national organization, the ADRDA has set a goal of educating the public. In fact, the ADRDA network has played a major role in NIA's public education activities directed to the general public, affected families, health professionals and others. Combined with ADRDA's materials on how to cope, PHS's publications on detection and diagnosis of senile dementia, as well as those on research advances and directions, contribute to a comprehensive packet of health education materials. ADRDA is fast making Alzheimer's disease a household word. They have also invested their time and effort in support of research.

Thank you, Mr. Chairman.

NINCDS

Alzheimer's Disease

Research Grants Currently Active on Alzheimer's Disease

Grant Number Institution Title Description	Principal Investigator	*Current Support
RO1 NS 12292-07 Medical University of South Carolina Aging, transport, and synaptic function in the CNS. This study measures the alteration of membrane transport in the nervous system as a function of aging.	Wheeler, D.D.	74,096
RO1 NS 14426-03 Indiana Univ.-Purdue Univ. at Indianapolis Selective neuronal loss and its sequelae: a model. This is a histologic and biochemical study of the Purkinje cell degeneration in a mouse mutant, as a model of selective cell loss in the nervous system.	Ghetti, B.	35,105
RO1 NS 14583-04 St. Paul-Ramsey Medical Center The role of GTPase in human brain. This study seeks to elucidate the role of GTPase in regulating the activities of adenylate and guanylate cyclase and of the microtubule polymerization system of human brain, systems possibly altered in Alzheimer's Disease.	Frey, W.	75,423
RO1 NS 15076-05 New York University Pathology and biology of neuronal fibrous proteins. This project is studying the biochemical interactions between neurofilaments, microtubles and their associated proteins and purifying paired helical filaments from Alzheimer's brains.	Shelanski, M.	135,336
RO1 NS 16242-03 Medical College of Pennsylvania Regulation of brain aminergic receptors in aging. This study is investigating the neuronal and hormonal factors that influence alpha- and beta-adrenergic brain receptors and determining the influence of age on brain tissue response to these factors.	Weiss, B.	115,388

* Current support includes fiscal year 1982 through June 8, 1983.

R01 NS 16278-04 Sidman, R. 173,045
Children's Hospital Medical Center Boston, Mass.
Reduced connections: cause of premature neuron aging.
This study will employ computer assisted graphics to characterize various elements in the mouse nervous system as a function of aging and investigate how altered connections affect cell loss.

R01 NS 17156-03 Katzman, R. 521,956
Yeshiva University
Senile dementia--Alzheimer and vascular.
Studies of Alzheimer's Disease (AD) and multi-infarct dementia (MID) in this project include: neuropeptide measurements, morphometric analysis, neuropsychometric analysis and diagnostic test development, mechanisms of learning and memory in AD, and a prospective study of risk factors in MID.

R01 NS 17479-01 Sar, M. 60,975
University of North Carolina
Hormone and neurotransmitter relationships in the brain.
These studies will define the anatomical relationships between steroid target cells and catecholaminergic and peptidergic systems of female rat brain to understand behavioral responses.

R01 NS 17487-02 Iqbal, K. 49,682
New York Institute for Basic Research
Alzheimer neurofibrillary tangles - biochemical studies.
These studies will determine the etiology and pathogenesis of neurofibrillary tangles of paired helical filaments, a hallmark of Alzheimer's Disease.

R01 NS 17535-02 Nixon, R. 95,206
McLean Hospital
Neurofilament proteolysis and Alzheimer's Disease.
This study will use new methods of proteolysis of neurofilament proteins in an animal model, in normal human brains and in Alzheimer's disease to determine the origin of paired helical filaments.

R01 NS 17822-02 Slatkin, D.N. 90,021
Brookhaven National Lab, New York
DNA turnover in human neurons.
These studies will determine the rate of DNA turnover in human cerebellar granular neurons which constitute 90% of the cerebellar cells and could be affected by nutrition.

R01 NS 18105-02 Grundke-Iqbal, I. 67,858
New York Institute for Basic Research
Alzheimer neurofibrillary pathology.
This study uses immunological techniques to study the neurofibrillary tangles and paired helical filaments of Alzheimer's Disease.

R23 NS 18361-02 Brady, S. 51,834
Case Western Reserve
Aging changes in subclasses of neuronal tubulin.
These studies will evaluate age-related changes during aging of nerve microtubules and tubulin.

R01 NS 18414-01 Coyle, J. 88,706
Johns Hopkins Medical School
Cortical cholinergic lesion/model for Alzheimer dementia.
These studies will define the neuroanatomy, synaptic chemistry, behavioral role, and pharmacology of the basal forebrain cholinergic projections innervating the neocortex and hippocampal formation.

R01 NS 18427-02 Baudry, M. 52,670
Univ. of California/Irvine
Pyruvate dehydrogenase and neuropathology.
This work will: develop techniques to manipulate pyruvate dehydrogenase (PDH), show how hippocampal denervation depresses PDH activity, reproduce Alzheimer pathology in cholinergic rat septum nucleus, and measure PDH effect on neuropathology.

R01 NS 18586-01 Krause, D. 146,723
City of Hope - California
Cerebrovasculature in vitro - neurotransmitters and aging.
This research is to understand the regulation of the cerebrovasculature by neurotransmitter systems through the use of in vitro biochemical and tissue culture techniques.

R23 NS 18675-01 Zackroff, R. 45,138
Northwestern University
Characterization of neural intermediate filaments.
This research will characterize intermediate filaments by: identifying their component polypeptides, determining their physical-chemical mechanism of assembly, comparing their different types, and analyzing their structural alterations in Alzheimer's Disease.

R01 NS 18851-02 Good, R. 147,225
Oklahoma Medical Res. Foundation
Pathogenesis of CNS and autoimmune disorders.
This study will examine the basis for primary immunodeficiency and determine if immunodeficiency and autoimmunity accompany Alzheimer's disease.

R13 NS 18890-01 Fisher, R. 7,500
Johns Hopkins Univ.
Conference for young neurological investigators.
This conference assembled young neurological investigators to examine and identify new approaches to the study of Alzheimer's disease.

R01 NS 19224-02 Gaskin, F. 119,287
Oklahoma Medical Res. Foundation
Biophysical studies on neurofibrous proteins in aging.
These studies will determine the factors required for the assembly and disassembly of neurofibrous proteins in brain.

R13 AG 03540 Watson, J. 10,000 (from NINCDS for shared support)
Cold Spring Harbor Laboratory
Cold Spring Harbor Symposium on Alzheimer's Disease.
This meeting of leading investigators in various fields discussed current research and treatment of Alzheimer's Disease and explored new research approaches to understanding its etiology and possible treatment.

Currently Active Research Grants Related to Alzheimer's Disease

Grant Number Institution Title Description	Principal Investigator	Current Support

P50 NS 03346-22 Plum, F. 222,384
(20% of total award)
Cornell University
Research Center in Cerebrovascular disease.
Experimental studies on blood-brain barrier (BBB) damaged by anoxia-ischemia and the relation of such damage to cerebral edema are being investigated.

P01 NS 03356-22 Suzuki, K. 176,909
(25% of total award)
Yeshiva Univ.
Brain development and developmental neurological disorders.
This is a multidisciplinary research program continuing the combined efforts of clinicians and basic scientists studying neurological diseases affecting brain development in both humans and experimental animals, and the basic neurological processes in brain development.

P50 NS 05820-17 Ginsberg, M.D. 77,000
(10% of total award)
University of Miami
Research Center for Cerebral Vascular disease.
Regional assessment of energy metabolism, blood-brain barrier function and histopathological alterations are being studied.

R01 NS 05961-17 Gilboe, D.D. 177,990
University of Wisconsin
Metabolism of the brain.
Transport of glucose, fatty acids, and drugs at the blood capillary cell interface using the indicator dilution method are being studied.

P50 NS 09649-12 Katzman, R. 71,822
(10% of total award)
Yeshiva University
Biogenic amines and neurological disorders.
This is a multidisciplinary research program continuing the combined efforts of clinical and basic investigations on dopamine, serotonin, and neuropeptide receptors to better understand their significance in diseased states.

R01 NS 09725-10 Duerre, J. 57,090
Univ. of North Dakota
Brain histone methylases.
These studies are investigating the regulation and enzymes which control the rate and extent of the methylation of chromosomal molecules and will possibly determine cellular ability to reproduce.

P50 NS 10939-11 Reivich, M. 101,119
(10% of total award)
Univ. of Pennsylvania
Cerebral blood flow and metabolism in stroke and shock.
The goal of this program is to determine the irreversible cerebral damage caused by various forms of hypoxia or ischemia and apply this information to the clinical situation.

R01 NS 12674-08 Manuelidis, E.E. 143,386
Yale University
Experimental Creutzfelt - Jakob Disease (hamsters, mice).
This study examines the pathogenesis of Creutzfelt-Jakob disease.

P01 NS 14069-06 Prusiner, S.B. 25,000
(10% of total award)
University of California, S.F.
Multiple Sclerosis and Viral Infection of the Central Nervous System.
This is a multidisciplinary study devoted to identifying the etiology, pathogenesis and treatment of these conditions.

R01 NS 14434-04 Huang, R. 81,527
Univ. of South Alabama
ESR study - Monoamine oxidase and membranes.
The purpose of this research is to better understand the function of monoamine neurotransmitters in brain and the mechanism of action of a number of adrenergic drugs.

R01 NS 14822-10 Marsh, R.F. 137,760
University of Wisconsin
Slow infection by unconventional viruses (mammals).
This study seeks to characterize the physiochemical nature of the unconventional agents producing spongiform encephalopathies in animals (scrapie and transmissible mink encephalopathy) and man (Creutzfelt - Jakob Disease).

R01 NS 16737-03 Hawkins, R.A. 115,889
Milton S. Hershey Medical Center
Hershey, PA
Regional blood-brain barrier transport of Amino acids.
Amino acid transport across the blood-brain barrier in pathological conditions is being examined to determine the location of changes in the capillary endothelial cells and their possible relevance to disease.

R01 17118-02 Dokas, L.A. 53,652
Medical College of Ohio, Toledo
Corticosterone and RNA metabolism in the hippocampus.
This study is to characterize neurochemical events in the hippocampus as a model of neuronal regeneration and relate the results to chemical and pharmaceutical approaches to long term stress, aging, and learning disabilities.

R01 NS 17252-03 Preskorn, S.H. 48,572
University of Kansas
Central adrenergic system and blood-brain barrier.
In using catecholaminergic blocker drugs, a technique is being developed to provide a reliable and inexpensive way to measure cerebral extraction of various substances.

R01 NS 17271-03 Vorbrodk, A.W. 42,246
N.Y. State Institute
Staten Island, N.Y.
Microvasculature in normal and pathological brain.
The goal is to study relationship between the localization of certain enzymatic activities and blood-brain permeability.

R01 NS 17701-02 Pardridge, W.M. 68,675
University of California, L.A., CA
Neuropeptides and blood-brain barrier (BBB).
This study proposes to examine peptide binding at the BBB using isolated cerebral capillaries as the primary model system and to devise method(s) for their transportation across the BBB.

R01 NS 17712-02 Nadel, L. 61,469
University of California, Irvine
Hippocampus and Cognition.
These studies attempt to elucidate the role of the hippocampal brain region in the thought process.

R01 NS 17848-01 Pearlmutter, A.F. 79,617
Medical College of Ohio, Toledo
Mechanisms of Vasopressin action in the brain.
The aim of this project is to study the binding of vasopressin and relate this information to learning and memory.

R01 NS 18030-02 Broadwell, R.D. 95,703
University of Maryland
The blood-brain barrier in normal and dimethyl sulfoxide (DMSO) - treated brain.
Enzyme cytochemical methodologies are being used to study the lysosomal system in cerebral microvasculature and pericytes; the search for a safe and effective means of opening the blood-brain barrier may depend on an increased understanding of the mechanism of barrier function as demonstrated in normal and DMSO treated animals.

R01 NS 18047-02 Koenig, H. 106,917
Northwestern, Chicago
Molecular pathology of blood-brain barrier breakdown.
The goals of this project are to correlate time course changes in ornithine decarboxylase and polyamine levels in isolated cerebral microvessels and brain parenchyma with changes in blood-brain barrier permeability.

R01 NS 18079-02 Lossinsky, A.S. 5,664
New York State Institute
Staten Island, N.Y.
Transport mechanisms in altered Blood-Brain Barrier.
The goal of this project is to study the relationship between two transport systems known to change their localization following blood-brain barrier damage.

R01 NS 18113-02 Houghten, R.A. 101,531
Scripps Clinic Lajolla, CA
Age-related changes in endorphin metabolism and receptors.
This research is studying changes in the processing and distribution of the naturally occuring opiate peptides, including endorphins, which have been implicated in a number of age-related and/or age-aggravated disease states such as obesity, decreased motivation, psychological disorders, sexual dysfunction, memory and learning disorders.

22-640 O—83——10

R01 NS 18362-01 Hogue-Angeletti, R.A. 117,661
University of Pennsylvania
Neurofilament structure.
This study proposes to isolate the constituent subunits of neurofilamentous proteins, the major cytoskeletal structure of large neurons, for structural analysis in order to obtain fundamental information about their nature, interactions and interrelationships, alterations of which are a major feature of Alzheimer's Disease.

R01 NS 18428-01 Coulter, H.D. 74,532
University of Minnesota
Neuropeptide immunocytochemistry of frozen-dried brain.
The long term objective of this project is to study the ultra-structural distribution of neuropeptides in the striatum, globus pallidus and substantia nigra, abnormalities of which have been implicated in a number of degenerative brain disorders.

R01 NS 18531-01 Stewart, J.M. 91,172
University of Colorado
Substance P and brain function: structure/activity.
This is a study of substance P, a neuropeptide implicated in muscle contraction, vasodilation, analgesia and alterations in learning and memory.

R01 NS 18775-01 DeBault, L.E. 80,124
University of Oklahoma
Vascular endothelium form and function - effects of glia.
The objective of this project is to evaluate the role of the glial cells in differentiation and maintenance of the blood-brain barrier capillary endothelium of the brain.

R23 NS 20006-01 Rainbow, T.C. 50,383
University of Pennsylvania
Gonadal steroid effect on neurotransmitter receptors.
This study is designed to understand how gonadal steroids modify the molecular properties of synapses and alter neuronal function, and to clarify more complicated forms of synaptic plasticity such as associative learning and memory formation.

P01 NS 16367-03 Martin, J. 419,935
(50% of total award)
Mass. General Hospital
Research centers without walls for Huntington's Disease.
This is a multi-institutional and multi-disciplinary research center using current information and developing new methodology in clinical and basic approaches to improve the diagnosis, treatment, prevention and understanding of the etiology of Huntington's Disease which should also help understand other degenerative brain disorders.

P01 NS 16375-03 Folstein, M. 257,953
(50% of total award)
Research Center Without Walls for Huntington's Disease.
This is a multi-disciplinary research center combining clinical and basic investigators to improve the diagnosis, etiology, mechanism, treatment and prevention of Huntington's Disease which should also help understand other degenerative brain disorders.

Positron Emission Tomography
(presented as 10% of total award)

Grant Number Institution Title Description	Principal Investigator	Current Support

P01 NS 14867-05 Reivich, M. 120,546
Univ. of Pennsylvania
Local cerebral glucose metabolism in man.
This research project is an interdisciplinary, interdepartmental collaborative effort to explore local cerebral glucose metabolism in man and how it is altered in various physiological and pathological situations such as stroke, epilepsy, brain tumor and Alzheimer's disease.

P01 NS 15080-04 Wagner, H. 44,036
Johns Hopkins Univ.
Program for study of neuroreceptor binding in man.
This interdisciplinary, interdepartmental study is directed toward in vivo localization of neuroreceptors, especially those in brain disease states.

R01 NS 15380-08 Wolf, A. 29,132
Brookhaven Natl. Lab. New York
Radiotracer R and D in nuclear medicine and neuroscience.
This research will continue to develop new technology in the preparation of positron emitters to be used for the study of brain metabolism.

P01 NS 15638-04 Wolf, A. 111,489
Brookhaven Natl. Lab., New York
Positron emitters and PETT in metabolic and neurological science.
This research will use tracers labeled with positron emitters and positron emission transaxial tomographs to map static and dynamic functions of the brain, particularly regional glucose metabolism in a variety of normal and pathological states in human and baboon brain.

P01 NS 15639-04 Lockwood, A. 58,129
Univ. of Miami
PET studies of cerebral metabolism and function.
These studies will include measurements of ammonia, glucose metabolism, regional cerebral blood flow and neurotransmitter function in various clinical conditions.

P01 NS 15654-04 Kuhl, D. 21,956
Univ. of Calif., Los Angeles
Neuroscience research using emission tomography.
These studies will quantify and localize cerebral biochemical patterns, especially glucose metabolism, in exploring the mechanisms underlying behavioral and neurological abnormalities.

P01 NS 15655-04 Beierwaltes, W. 84,363
University of Michigan
PET study and biochemistry and metabolism of the CNS.
These studies will utilize established positron emitting probes and synthesize new radiopharmaceutical probes to non-invasively evaluate human brain metabolism in various disease states.

P01 NS 15665-04 Posner, J. 72,074
Sloan-Kettering, N.Y.
Positron emission tomography of the CNS.
This project will elucidate the effects of neurological disease, age and dementia on brain metabolism.

P50 NS 06833-16 Raichle, M. 60,177
Washington Univ., St. Louis
An interdisciplinary stroke program.
This study will elaborate the metabolic and hemodynamic status of the brain using positron emission tomography.

P50 NS 10828-08 Taveras, J. 105,853
Mass. General Hosp.
An interdepartmental stroke program.
This project explores the clinical application of positron emission tomography to cerebrovascular disease in determining the reversibility of neural defects by therapeutic intervention.

Currently Active Research Contract

Grant Number Institution Title Description	Principal Investigator	Current Support
Y01 NS 0004 East Baltimore Epidemiology Catchment/Dementia Study. This project is a clinical and sociological evaluation of non-institutionalized dementia patients.	Eaton, W.	175,000

Intramural Research Related to Alzheimer's Disease

Project Number Research Unit Title Description	Principal Investigator	Current Support
Z01 NS 00200-28 CN/IRP/NINCDS Cognitive and Emotional Profile of Neuropsychiatric Disorders. Memory, learning and perception are evaluated and collate with biochemical measures in individuals with Alzheimer's Disease, Huntington's Disease and "at risk" for Huntington's Disease.	Fedio, P.	112,621
Z01 NS 00969-18 (10% of total) CNSS/IRP/NINCDS Chronic CNS Disease Studies: Slow, Latent and Temperate Virus Infections. These studies elucidate the cause and pathogenesis of chronic degenerative central nervous system disorders.	Gajdusek, C.	158,994
Z01 NS 01245-17 CN/IRP/NINCDS EEG Learning Correlates Using Scalp and Intracranial Depth Electrodes. This is an electrophysiological study of information processing in the human brain in normal subjects and Alzheimer's patients.	Fedio, P.	26,499

Z01 NS 02240-06 Schoenberg, B. 198,742
OD/IRP/NINCDS
Epidemiology of Dementia.
A number of approaches are being used to estimate the mortality and morbidity of Alzheimer's disease/senile dementia in several population groups in the U.S.

Z01 NS 02265-06 Chase, T.N. 281,551
ET/IRP/NINCDS
Pharmacology, Biochemistry and Physiology of Central Neurotransmitters.
This project consists of clinical and preclinical investigations seeking to elucidate how the activity of specific transmitter systems relate to neuropsychiatric function.

Z01 NS 02315-05 DiChiro, G. 115,933
SNB/IRP/NINCDS
(50% of total)
Positron Emission Tomography
This laboratory has constructed a high-resolution scanner called the Neuro-PET and has used this scanner to examine the brains of patients with brain disease.

Z01 NS 02361-05 Spatz, M. 39,748
LNNS/IRP/NINCDS
Investigations on blood-brain barrier (BBB) permeability.
The enhancement of protein permeability is being investigated in bilateral cerebral ischemia induced by occlusion of the carotid arteries.

Z01 NS 02370-04 Schoenberg, B. 56,310
(10% of total)
OD/IRP/NINCDS
Racial Differentials in the Prevalence of Major Neurologic Disorders and Surveys in Developing Countries.
This study will accurately document possible racial differentials in the prevalence of major neurological disorders by surveying an entire country.

Z01 NS 02518-01 Martinez - Maldonado, E. 2,489
OBFS/IRP/NINCDS
Neurological Aspects of Aging in Primates.
This is a multidisciplinary approach to study the neurological aspects of aging in Macaco mulattas.

Research Training

In addition to its extramural research grant program, its contract program and its intramural research program, the NINCDS in 1982 estimates manpower development program support of $1,024,997 including: Teacher Investigator Development Awards of $268,967, Research Career Development Awards of $86,030, and National Research Service Awards of $670,000.

Senator GRASSLEY. Dr. Ringler, as Acting Director of the Institute on Aging, you are undoubtedly aware that in 1979, the NIA took the lead role in formulating the health research initiative on the dementias of aging in an effort to coordinate the activities of those Federal organizations involved in research in this area. Would you characterize the National Institute on Aging as the lead agency in the Alzheimer's research area?

Dr. RINGLER. Mr. Chairman, Secretary Heckler has indicated that the newly established Interagency Task Force on Alzheimer's Disease will be the focal point within the Department of Health and Human Services, and we are very happy to participate and play a very active role on the task force. We are extremely pleased that the Secretary is so interested in this area.

Responding more directly to your question, the report that I referred to earlier is an outgrowth of the initiative that you mentioned, where the National Institute on Aging did play an important role in coordinating activities having to do with Alzheimer's disease, since this is a major problem that affects the elderly.

So, with the NINCDS and the NIMH, the NIA has generated this report over the past couple of years.

Senator GRASSLEY. I would like to have either you, Dr. Ringler, or anyone else, comment on what you foresee as the anticipated outcome of the task force that has been recently created.

Dr. GOLDSTEIN. Bob, why don't you go ahead?

Dr. RINGLER. I think we look forward to this task force with considerable enthusiasm. We have had one meeting, as the Secretary indicated. I would see the outcome of the task force as an attempt to assess very carefully what is ongoing, first of all, within the Department. I think the three of us here have a pretty good familiarity with that to begin with. Perhaps more importantly, I think the task force will try to chart a course for the future—what the Secretary calls a strategy for the future—in this particular disease area. I think perhaps as important, or even more important, is the fact that the Secretary also wishes the task force to integrate the research findings with the areas of policy development and health care financing. To that latter end, the Health Care Financing Administration is also involved in the task force. So it will be a channel of communication within the Department that goes beyond the usual limitations of research.

Dr. PARDES. Senator, I think that the forming of this task force signals important new national attention to this disorder, and the fact that Secretary Heckler has chosen this as one of the first actions she has taken is highly significant. When it is known within the Department that the Secretary and also congressional leaders are concerned about a given issue, people throughout the Department, whether it is the budget or legislative channels, or in the research institutes, work that much more energetically toward trying to solve that particular problem.

Now, we are sensitive to the fact that you cannot make research happen just by appropriating funds. But the task force would insure that any research opportunities that were in front of us would be adequately funded. The task force would also look for any unique strategies for dealing with the variety of issues that surround Alzheimer's disease, and as Dr. Ringler said, this would

insure coordination among the variety of enterprises within the Department and in other areas of Government working on this problem, because sometimes, one person's idea is the very stimulus for another person's creative spurt. So we are extremely enthusiastic about this research effort. We believe this task force will be a focal point for a broad governmental effort to move forward our knowledge in this area.

Dr. GOLDSTEIN. I can only reconfirm what my colleagues have said, and put it in the context that there are at least three windows toward research on Alzheimer's disease: The neurological window, the behavioral science and psychiatric window, and the window which encompasses research into the societal impact of this disease. What the task force provides for the three institutes at this table is an opportunity to examine each other's windows, to begin to understand what the leads are, and therefore to coordinate our approaches in the most effective manner. And so, Mr. Chairman, I think the task force provides us with an opportunity to do our job better.

Senator GRASSLEY. Dr. Goldstein, do you have any views or preferences on the earmarking of funds for Alzheimer's disease research—and I referred previously to what this committee has done in that area and what the House committee has done in that area.

Dr. GOLDSTEIN. Sir, I honestly believe that we do not know just where the research breakthroughs that we all hope for will occur. It may be in immunology; it may be in the area of genetic programing. Earmarking essentially baacks research into a corner. My own opinion, Mr. Chairman, is that we would be better off moving ahead in this area without earmarking, giving the scientists and the scientific leaders the best opportunity to pursue all leads, rather than only those specified in the earmarking.

I believe that the best way that we can move forward with research in this area is not through earmarking.

Senator GRASSLEY. As a matter of time, I have two further questions I want to ask Dr. Pardes, but I will submit these to you in writing. One deals with whether or not you are planning another international conference as you previously had, and the other one would be the prevalence of the disease and the level of research outside the country, but I think for time's sake, I had better pass those up, and we will submit them to you in writing so you will know exactly what we want.

Dr. PARDES. I would be happy to respond to you in writing.

Senator GRASSLEY. Thank you.

[The questions and responses of Dr. Pardes follow:]

United States Senate

COMMITTEE ON LABOR AND
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WASHINGTON, D.C. 20510

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June 4, 1983

Herbert Pardes, M.D.
Director, National Institute of
Mental Health
Alcohol, Drug Abuse, and Mental
Health Administration
Rockville, MD 20857

Dear Dr. Pardes:

Thank you again for your testimony before our subcommittee in the area of Alzheimer's disease.

Due to time constraints, we were unable to benefit from any statements you may have had regarding the following areas which we will include in our hearing record:

1. In 1968, the Center for Studies of the Mental Health hosted an international conference on the clinical aspects of Alzheimer's disease and Senile Dementia. Is another conference planned? My understanding from your testimony is that research from this and another conference was published and is considered a standard resource in the field. Would this publication be beneficial for this hearing record?

2. What is the prevalence and the level of research of Alzheimer's disease outside the United States?

In addition to these statements, I believe that our record will benefit from a breakdown of grants that each Institute currently utilizes in the research of Alzheimer's disease.

I look forward to hearing from you.

Sincerely,

Chuck Grassley

Charles E. Grassley
Chairman, Subcommittee on Aging

CEG:mb

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Alcohol, Drug Abuse, and
Mental Health Administration
National Institute of Mental Health
Rockville MD 20857

1983 JUN 30 AM 8 A5
JUN 23

The Honorable Charles E. Grassley
Chairman, Subcommittee on Aging
United States Senate
Washington, D.C. 20510

Dear Senator Grassley:

Thank you for your letter of June 4 inquiring about my testimony on Alzheimer's disease before the Subcommittee on Aging.

In 1978, The Center for Studies of the Mental Health of the Aging, National Institute of Mental Health (NIMH), hosted an international conference on The Clinical Aspects of Alzheimer's Disease and Senile Dementia, in collaboration with the National Institute of Neurological and Communicative Disorders and Stroke, (NINCDS) and with the National Institute on Aging, (NIA). The proceedings of this conference were edited by Drs. Nancy E. Miller and Gene D. Cohen, and published by Raven Press in 1981. While it probably is not feasible to include the entire 357-page volume in the hearing record, you may find it useful to print certain selections from the text. Accordingly, I have enclosed from this volume copies of the introductory statements from the Institute Directors of NIMH, NINCDS, and NIA, respectively. I have also enclosed a copy of the introductory chapter by Dr. Miller and Dr. Cohen, which reviews the book's major substantive issues, highlights new and important research questions, and consolidates what is presently known about the humane and appropriate management and care of the elderly individual with Alzheimer's disease. The proceedings from an earlier conference entitled Alzheimer's Disease: Senile Dementia and Related Disorders, edited by Drs. Robert Katzman, Robert D. Terry, and Katherine L. Bick, and published by Raven Press in 1978, focused more heavily on the possible causes of this disorder rather than on management, assessment, and treatment. I have enclosed the table of contents and list of contributors from each of these volumes on Alzheimer's disease for your information. Although no further conferences on Alzheimer's disease are being planned in the immediate future, it is highly probable that plans will soon be under way for convening future workshops and conferences in this area. At the same time, there are a number of related conferences emerging from the field, and typically the national Institutes participate in these.

As to the prevalence of Alzheimer's disease outside the United States, data is sketchy, with the best data perhaps coming from Great Britain where the prevalence of the disorder seems similar percentagewise to that of the United States.

Regarding your question concerning research outside the United States in this area, it is clear that most of the major discoveries in understanding Alzheimer's disease have emerged from laboratories in the United States, Great Britain, and Sweden. The level of research on Alzheimer's disease in those countries together appears roughly similar to that in the United States. Recently there has been growing research interest in Alzheimer's disease expressed by a number of countries, and in view of such interest, The World Health Organization will be sponsoring a special meeting in this area in Paris, France, in August 1983.

As you requested, I am enclosing a comprehensive listing of all currently supported departmental research activity in the area of Alzheimer's disease and senile dementia. Included are the names of the principal investigator, his/her institutional affiliation, the title of the project, and dollar amount.

Please let me know if I can be of any further assistance in this important enterprise.

Sincerely yours,

Herbert Pardes, M.D.
Director

Enclosures

ENCLOSURE # 1

Clinical Aspects of Alzheimer's Disease and Senile Dementia, (Aging, Vol. 15), edited by Nancy E. Miller and Gene D. Cohen. Raven Press, New York 1981.

Introductory Statement: A View from National Institutes of Health

Donald S. Fredrickson

National Institutes of Health, Bethesda, Maryland 20205

This volume represents the continuation of an exploration of the state of knowledge about Alzheimer's disease and senile dementia that was initiated in 1977 by the same sponsors. Its emphasis on the clinical aspects of these problems will, once again, be rooted in the findings of research and focus on what is known, but at the same time and perhaps in a more forcible way, bring us face to face with what is not known.

Joint sponsorship of these proceedings by the concerned Institutes—in this case crossing major organizational lines—exemplifies the kind of collaboration that enhances the efforts of each participating unit in dealing with different aspects of a common endeavor.

The dementias and their devastating human consequences constitute a significant public health problem of great economic dimensions. They primarily affect older people, a group that now constitutes 11% of the population and is responsible for 30% of the health care costs in this country. Brain deterioration represents perhaps the most critical aspect of aging, leading to loss of independence, withdrawal from active life, and often to institutionalization. It is one of the major reasons for admission to nursing homes—an extremely costly element in the nation's health bill.

It is predicted by the year 2000 there will be 32 million people over 65 years of age or 12% of our nation's population, and the number of the very old—those 75 and above—will be anywhere from 12 million to 18 million, depending on trends in mortality rates. So we are concerned here with a very substantial number of people and a huge economic burden.

If we can prevent or reverse some of the consequences of Alzheimer's disease and senile dementia, if we can improve diagnosis and clinical management, and if we can avoid or postpone institutionalization for even a small segment of the older population, we will be making a tremendous contribution to reducing the burden of medical care costs for the American people. Even more important, we will have made life better for all.

In the spring of 1978, the National Institutes of Health, together with the health-related agencies of the Department of Health, Education, and Welfare, began an intensive effort to develop a set of research principles to guide in

the planning process by which the varied and substantial resources of the Department can be brought to bear on the nation's health needs.

This series of papers embodies precisely the intent of the planning principles—a commitment to fundamental research, and a recognition of the need not only to acquire new knowledge, but also to validate and apply it.

From such considerations, the National Institutes of Health has adopted research and research training in Alzheimer's disease and the dementias of aging as a special initiative. These Institutes are involved. The National Institute on Aging conducts research on basic science and clinical aspects of regional brain metabolism, neurochemistry and pharmacology. The major research effort of the National Institute of Neurological and Communicative Disorders and Stroke is to define etiology and pathogenesis and, in attempting to accomplish this, the Institute conducts clinical research projects, therapeutic trials, and epidemiologic studies. The possible role of a latent or slow virus in chronic dementia is being explored by the National Institute of Allergy and Infectious Diseases.

The total NIH financial commitment to Alzheimer's diesease and the dementias of aging increased from less than 7.5 million in fiscal 1979 to almost 11 million dollars in 1980 and the upward trend will be continued. These efforts, in coordination with those of ADAMHA, our sister agency, and of the scientific community at large, should certainly lead to more effective treatment and, I believe, the prevention of some of the dementias.

Clinical Aspects of Alzheimer's Disease and Senile Dementia, (Aging, Vol. 15), edited by Nancy E. Miller and Gene D. Cohen. Raven Press, New York 1981.

Introductory Statement: Mental Health Perspectives

Herbert Pardes

National Institute of Mental Health, Rockville, Maryland 20857

With recent advances in the absolute number and relative proportion of older persons in the general population, growing attention has been focused by federal agencies on the devastating and disabling effects of those brain disorders that are associated with advancing chronological age. Among these disorders, senile dementia of the Alzheimer's type has been estimated to affect more elderly persons than any other brain disease, with 4 to 15% of the population over 65 being affected. Although the aged are disproportionately subject to mental and emotional problems, it is the individuals over 75 years of age, who are most vulnerable to the development of mental disorder, who also comprise the fastest growing segment of the elderly population.

The National Institute of Mental Health (NIMH), a component part of the Alcohol, Drug Abuse, and Mental Health Administration in the Public Health Service, is responsible for implementing the nation's major program in research and training for enhancing mental health and for understanding, treating, and preventing mental illness. In view of the great need for more fundamental information about how individuals function and fail to function, both emotionally and cognitively, in middle and later life, NIMH has actively embarked on a program of support to stimulate researchers to study these problems.

At NIMH, the Center for Studies of the Mental Health of the Aging (CSMHA) is the focal point for work in aging and the late life dementias. The major role of the Center is to stimulate, coordinate, and support research, training, and technical assistance efforts relating to aging and mental health. The Center, under the leadership of Dr. Gene D. Cohen, supports a wide-ranging, multidisciplinary set of studies that have both theoretical and applied implications. These include studies of the etiology, diagnosis, natural history, course, and prevention of mental disorders in later life, with special emphasis on the spectrum of dementias, affective disorders, and the interface between physical disease and psychiatric illness. The Center's interests range from support of studies applying advances in computerized axial tomography to problems in differential diagnosis, to systematic investigations of the role of the family in sustaining the psychological integrity of the patient with Alzheimer's diesease who is living in the community.

Other sections of NIMH also regard the mental health of the aging as a high priority area, and collaborate with CSMHA in the support and stimulation of innovative research. Psychopharmacology, for example, represents a rapidly advancing field of research, which has the potential for uncovering new clues in the etiology and basic mechanisms of the disease process itself. Studies are underway at the Psychopharmacology Branch at NIMH to measure the effects, for example, of naturally occurring substances such as small brain peptides on memory in senile dementia. The possible effects of increasing cholinergic activity on mental deficits associated with Alzheimer's disease are also being investigated, as are the effects of vasodilators, ergot alkyloids, and a variety of other psychotropic compounds.

The CSMHA also collaborates with the Biometry and Epidemiology Branch in fostering investigations that examine the distribution of late life dementias in the general population. Epidemiologic studies are urgently needed to define the prevalence, incidence, and risk factors associated with this disorder since available estimates of the incidence and prevalence of senile dementia are based on a patchwork of noncomparable studies. The absence of appropriate epidemiologic data therefore continues to be a major hinderance to the effective planning of appropriate health and mental health services for the elderly. In the context of its major Epidemiologic Catchment Area initiative, the Center for Epidemiologic Studies, in collaboration with the CSMHA and the National Institute on Aging, plans to oversample the elderly living in both institutions, and in the community, in various geographic regions of the United States. There is also interest in evaluating the interplay of genetic and environmental factors on the expression of symptomatology in dementing illnesses. One recent epidemiologic investigation supported by NIMH revealed that relatives of probands with histologically confirmed Alzheimer's disease manifested excessive morbidity from Alzheimer's disease, Down's syndrome, and hematologic malignancies. These findings raise the specter of a common genetic deficit in the development of Alzheimer's diesease, Down's syndrome, and various malignancies, and point the way to possible etiologic mechanisms.

Other portions of the Institute also play important roles in advancing investigations of the psychopathology of later life. As one of its many foci, the Clinical Research Branch, for example, supports studies on the nature, specificity, and efficacy of psychological interventions on various types of mental illness, including conditions of altered brain function, and the Mental Health Services Development Branch assists in the formulation of innovative approaches to mental health service delivery, including a focus on elderly persons with brain impairment.

As a scientific research institute, NIMH is rather unique in its mandate to provide support not only for research training, but also for services, and for the clinical training of mental health professionals. Critical to the advancement of understanding, prevention, and treatment of these late life disorders is the presence of an adequate pool of high caliber professionals, both researchers and clinicians, who are knowledgeable regarding the diagnostic and therapeutic

dilemmas presented by the dementias of late onset. Programs sponsored by both the Center for Studies of the Mental Health of the Aging and the Division of Manpower and Training are currently underway in an effort to increase the number of geriatric specialists in the core mental health disciplines.

At the intramural level, a new research unit in Geriatric Psychiatry has been set up under the direction of Dr. Richard Jedd Wyatt. The unit has shown impressive progress in studies of neuroplasticity and in pharmacological research. This group has also been involved in the development of new and sensitive methods for measuring aluminum, a neurotoxin, and in research on slow viruses, in collaboration with the National Institute of Neurological and Communicative Disorders and Stroke. Extramurally, the relationship of hypertensive disease to dementia is being examined as part of a long-term clinical trial supported jointly by the National Heart, Lung, and Blood Institute, the National Institute on Aging, and the National Institute of Mental Health.

A major area of NIMH's interest is in the development of improved models for integration of mental health with health services. Full access to mental health services for those needing care constitutes a high priority Institute goal. Underserved populations, especially elderly persons with cognitive disorders, who have received only minimal treatment in the past, will be especially represented in this initiative. From another angle, the treatment and care of the chronically mentally ill, including individuals with senile dementia of the Alzheimer's type, is of special concern both to NIMH and throughout the Department of Health and Human Services. This attention would include a focus on those patients with psychopathology addressed in the Mental Health Systems Act, as well as those encompassed in the newly developed National Plan for the Chronically Mentally Ill. In addition to the broad scope of these activities, and to an expanding HHS interest in the quality of long-term care, there is the proposed federal initiative specifically focused on Alzheimer's disease and the dementias of aging, which will bring together the combined resources of the National Institute of Mental Health, the National Institute on Aging, the National Institute of Neurological and Communicative Disorders and Stroke, and the National Institute of Allergy and Infectious Diseases.

In conclusion, although the etiology of these dementias, in most cases, remain unknown, although their diagnosis remains problemmatic, and their effects on the family—in disrupting human ties, in causing the loss of productive members of society, and resulting in profound social and emotional hardships—are great, much effort, thought, and fresh initiative is being brought to bear on this devastating public health problem, on the part of the National Institute of Mental Health, and its sister agencies and Institutes, across the span of the Public Health Service. The opportunities for finding new solutions for this crippling disorder have never been brighter.

Clinical Aspects of Alzheimer's Disease and Senile Dementia, (Aging, Vol. 15), edited by Nancy E. Miller and Gene D. Cohen. Raven Press, New York 1981.

Introductory Statement: Neurological Perspectives

Donald B. Tower

National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, Bethesda, Maryland 20205

At the first conference of Alzheimer's disease–senile dementia, I pointed out a number of neurobiological aspects that represent intriguing and urgent research challenges (7). In particular there is the very special relevance to the overall problem of aging of the human nervous system, with the likelihood that aging of most of the body is a function of the "health" of the nervous system. Thus, we of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) recognize a close identification with the many problems confronting the National Institute of Aging (NIA), and indeed we are engaged in a continuing dialogue with our colleagues in the NIA over this and many other program concerns.

In this volume we begin consideration of the clinical aspects of the dementias, where the interests and responsibilities of the NINCDS clearly overlap those of the National Institute of Mental Health (NIMH). Since the inception of these two institutes more than 25 years ago, we have tended to divide research responsibilities between the neurosciences (NINCDS) and the behavioral sciences (NIMH). As Dr. Klerman has already indicated, these distinctions are hardly tenable today. The borders have become blurred as those in behavioral studies are confronted with biochemical circuitry, modulatory peptides and hormones, and neuropharmacological agents that have specific correlations with behavioral phenomena. At the same time neuroscientists are forsaking the simpler neuronal networks and electrophysiology for the problems of central processing, adaptation, plasticity, and all those complex integrative functions that comprise behavior. Nowhere is the confluence of the two streams of research more critical than in the problems posed by the human dementias.

Among the clinical problems presented by the dementias, we at the NINCDS view at least three as particularly important. First, there is the sheer magnitude of the problem in terms of numbers of patients—an aspect discussed at some length in the first conference (6). Secondly, there is the currently perplexing variety of dementias encountered in clinical neurological and psychiatric practice.

There is the dementia that develops in Huntington's disease—a genetically determined autosomal dominant disorder characterized by massive destruction

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of neurons in the striatum and consequent involvement of cerebrocortical neurons (1). There is the population focus of Parkinson-dementia among the native Charmorros on Guam—a disorder in which the parkinsonism can be effectively managed with L-DOPA and its congeners without affecting the relentless course of the dementia, and in which there are neuropathological changes characteristic not only of Parkinson's disease but also of Alzheimer's disease (5). There is the slow-virus group of disorders—the transmissible spongioform encephalopathies, like Kuru and Creutzfeldt-Jakob disease, in which dementia is the final expression of the destruction of neurons in many gray matter areas, together with pronounced astroglial changes (4). And there is the Alzheimer-senile dementia group of disorders under specific consideration here.

This is not an exhaustive list, but even these examples illustrate some of the epidemiological, etiological, and clinical dilemmas. And these are too often complicated by vascular, nutritional, visual, and auditory disorders that plague the aging population. Moreover, many such patients commonly go to the neurologist, although they have major behavioral components that warrant sharing with the psychiatrist—or vice versa. We hope that new research approaches like positron emission transverse tomography (PETT) will be instrumental in unravelling some of the unknowns in these peculiarly human disorders. What CT scans have done for the demonstration of morphology and pathology in the living human brain, the PETT scans will do for metabolism and function (3). For the first time, we are promised an opportunity to probe harmlessly in the living patient's brain the mysteries of such peculiarly human disorders as the dementias.

Finally, the dementias confront all of us with major catastrophes in patient care and services. In this respect each of the examples just cited are all too familiar to the neurologist, the psychiatrist, and the gerontologist. During the public hearings recently held by the Congressionally mandated National Commission on Huntington's Disease, those of us who attended such hearings heard over and over again the destruction wreaked on families, their financial disasters, and the often fruitless search for medical help and institutional care that the havoc of the Huntington's disease dementia creates (2). And Huntington's disease is by no means unique in these respects. Thus, the needs for research that will provide the clinician with preventive, screening, counselling, and therapeutic measures are obvious. But until these measures become realities, we must deal with the dementias by providing regional, comprehensive centers for care and services as well as providing effective solutions to the financial and institutional care problems.

Thus, from the NINCDS perspective we emphasize three points: the continuum of research from basic mechanisms and animal models in the laboratory to the clinical problems at the patient's bedside; the essential pooling of research talents and resources by the concerned institutes—NINCDS, NIA and NIMH; and the imperatives for all of us in DHHS to address the acutely desperate needs in the areas of patient care and services.

This conference-workshop must develop advice and recommendations for planning clinical research, management, and services, and for the allocation of necessary resources. The problems are important and immense; the challenges are extraordinary. I cannot emphasize too strongly that for our older citizens especially, the health of the nervous system is *the* critical factor in the quality of their lives.

REFERENCES

1. Chase, T. N., Wexler, N., and Barbeau, A. (eds.) (1980): *Second International Huntington's Disease Symposium.* Raven Press, New York.
2. Commission for the Control of Huntington's Disease and Its Consequences (1977): *Report, Vol. I: Overview* (DHEW Publication (NIH) 78–1501) U.S. Dept. Of Health, Education, and Welfare-PHS-NIH, Bethesda, Maryland.
3. Fox, J. L. (1978): Methods map brain functions chemically. *Chem. Engineer. News,* 56:20–22.
4. Gajdusek, D. C., and Gibbs, C. J., Jr. (1975): Slow virus infections of the nervous system and the laboratories of slow, latent and temperate virus infections. In: *The Nervous System, Vol. 2: The Clinical Neurosciences,* edited by T. N. Chase and D. B. Tower, pp. 113–135. Raven Press, New York.
5. Hirano, A., Malamud, N., and Kurland, L. T. (1961): Parkinsonism-dementia complex, an endemic disease on the island of Guam. II. Pathological features. *Brain,* 84:662–679.
6. Katzman, R., Terry, R. D., and Bick, K. L. (eds.) (1978): *Alzheimer's Disease: Senile Dementia and Related Disorders.* Raven Press, New York.
7. Tower, D. B. (1978): Alzheimer's disease-senile dementia and related disorders: Neurobiological status. In: *Alzheimer's Disease: Senile Dementia and Related Disorders,* edited by R. Katzman, R. D. Terry and K. L. Bick, pp. 1–4. Raven Press, New York.

Clinical Aspects of Alzheimer's Disease and Senile Dementia, (Aging, Vol. 15), edited by Nancy E. Miller and Gene D. Cohen. Raven Press, New York 1981.

Introductory Statement: Aging Perspectives

Robert L. Ringler

National Institute on Aging, National Institutes of Health, Bethesda, Maryland 20205

In the United States, the elderly constitute one of the fastest growing segments of the population. The 24.4 million persons over 65 make up just over 11% of the population (8), and we expect that this figure will jump to the range of 17 to 21% by 2030 (2). More striking than this is the rate at which the elderly population is growing compared with the population at large. Between 1970 and 1977, the number of persons 65 and over increased by 18%, whereas the general population increased by only 5% (1).

As a response to the dramatic increase in the total number of elderly, the U.S. Congress passed the Research on Aging Act early in 1974, thereby creating a National Institute on Aging (NIA) to conduct and support biomedical, behavioral, and social research to improve the quality of life in the later years.

Health care professionals are also beginning to appreciate the significance of the changing age structure. Faced with a growing number of elderly patients, physicians are becoming more aware of the dangers of accepting negative stereotypes of old age and more concerned with providing effective treatment for the special needs and problems of the aged.

Despite many advances and many positive changes in attitudes toward the elderly, however, research on the chronic dementias of aging has been comparatively neglected. The belief that these disorders are both inevitable and intractable continues to prevail.

The NIA supports the position that the dementias are not concomitant with old age; rather, they represent pathological disease states that should be subject to investigation, skilled diagnosis and treatment, and, given further research, preventive activities.

In keeping with the Institute's goal to enhance the quality of life in the later years, the NIA considers research toward an understanding of senile dementia to be a major priority. Approximately 1 million people in the United States over age 65 suffer severe dementia with global intellectual deterioration and inability to carry out the normal tasks of daily living. An additional 2 to 3 million are mildly or moderately affected. Of these, it is estimated that between 500,000 and 1.5 million persons suffer from senile dementia of the Alzheimer's type—so called because clinical presentation, postmortem pathology, electron microscopy, and histochemical studies all support the concept that senile demen-

tia and Alzheimer's disease are indistinguishable with the exception of age of onset (4).

In an effort to serve as a catalyst for research in this area, the NIA joined with the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the National Institute of Mental Health (NIMH) in sponsoring the first conference of this series (5). Since that time, the NIA has instituted a neuroscience program both extramurally and intramurally.

Last year, the extramural neuroscience element—which supports research at universities, medical centers, and other research institutions—funded several significant research projects dealing with senile dementia and with age-related changes in the central nervous system. One NIA-supported study in animal models is already yielding data suggesting that the brain may be able to compensate for some forms of cell loss (6). Since many older persons suffer death of neurons, which is also one of the hallmarks of senile dementia, this is an area deserving of further research. In other studies of major import, scientists are developing a better understanding of structural and neurochemical changes that accompany senile dementia in human research subjects.

Also, in this past year, Dr. Stanley I. Rapoport, who is well-known for his work on the blood-brain barrier, became the first director of the Laboratory of Neurosciences at NIA's intramural research facility in Baltimore. The importance of continued research on the barrier can hardly be exaggerated, particularly in light of our interest in the etiology of senile dementia. The barrier normally provides selective nutrition for the brain, excludes antibodies from the brain that could kill cells or alter function, and may play a role in viral passage.

One collaborative project currently being planned involves using positron emission transverse tomography to study cerebral metabolism in humans, specifically, the uptake of an analog of glucose. Using this noninvasive technique, NIA investigators can measure functional changes in the brain activity of persons with Alzheimer's disease or senile dementia, as well as persons who are aging normally.

Many of the participants at the first conference of this series noted that the baseline data necessary for scientific study of senile dementia are not available. Under the direction of Dr. Jacob Brody, the NIA has now established an Epidemiology, Demography, and Biometry Program to develop information on the incidence and prevalence of senile dementia and other diseases that afflict the old. Currently, most older people escape all medical and statistical attention; as a result, health planning is often based on incomplete information.

To develop valid and reliable quantitative instruments and measures of dementia, and to determine the magnitude of the problem, Dr. Brody is collaborating with clinical and laboratory scientists and epidemiologists at NIMH, NINCDS, and NIA, as well as internationally renowned investigators such as Sir Martin Roth of Great Britain.

The NIA Epidemiology, Demography, and Biometry Program is also collaborating with epidemiologists at the NINCDS in supplementing the NIMH popula-

tion or catchment area studies of community mental illness being directed by Jerome Myers of Yale University.[1] The goal is to determine the number of older people with senile dementia who have remained in the community.

Dr. Brody also hopes to join NINCDS in its study of amyotrophic lateral sclerosis-parkinsonism dementia complex in Guam. Neurofibrillary change, which is a common histological feature of senile dementia of the Alzheimer's type, is also seen extensively in the brains of those suffering from the severely debilitating and progressive dementia, which is essentially indigenous to the Chamorro population of Guam.

On the clinical side, NIA supports the position that health care professionals must rule out the possibility of a treatable disorder before establishing a diagnosis of Alzheimer's disease/senile dementia. Although there are numerous references in the medical literature to the physiological and psychological disorders that can mimic senile dementia, the NIA initiated a special effort to develop guidelines for the diagnosis and treatment of mental impairment in the elderly (7). It is tentatively estimated that such disorders may account for as much as 30% of those cases diagnosed as irreversible, with untold institutional costs.

At the same time, we look forward to the development of clinical programs designed to test treatment modalities for the so-called irreversible disorders. These disorders are by no means hopeless ones.

Before closing, I would like to highlight a very positive development of this past year. Until recently, the victims of Alzheimer's disease/senile dementia and their families have had to cope as best they could. When suddenly faced with a diagnosis of Alzheimer's disease—often after years of going from one physician to another—they were given little hope or information. When trying to care for the affected person at home, the family was given minimal support. In addressing this group last year, Dr. Robert N. Butler advocated the founding of an organization to aid the families of persons with Alzheimer's disease in facing the personal and financial crisis this often entails, as well as the disruption of family life (3). Several such groups have now formed to assist the family and increase public awareness of the need for research support for the dementias.[2]

Much has been accomplished since the meeting a year and a half ago, but there is still a need to increase our fundamental knowledge of the chronic dementias through basic, clinical, behavioral, and epidemiologic research; and to apply that knowledge to improved health care. The National Institute on Aging sincerely believes that joint efforts such as this meeting represent one approach to the attainment of the overall goal of ameliorating or preventing the dementias of aging.

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[1] Myers, J., The Epidemiologic Catchment Area Program. (National Institute of Mental Health grant U01-MH-34224.)

[2] In October 1979, seven self-help groups dealing with Alzheimer's disease and related disorders in Boston, New York, Pittsburgh, Minneapolis, Columbus, Seattle, and San Francisco united to form the Alzheimer's Disease and Related Disorders Association (292 Madison Avenue, New York, New York 10017).

REFERENCES

1. Brotman, H. B. (1978): The aging of America: A demographic profile. *Natl. J.*, 10:1622–1627.
2. Bureau of the Census (1978): *Demographic Aspects of Aging and the Older Population in the United States.* (Special Studies Series P-23, No. 59). U.S. Government Printing Office, Washington, D.C.
3. Butler, R. N. (1978): Alzheimer's disease—senile dementia and related disorders: The role of NIA. In: *Aging: Vol. 7: Alzheimer's Disease: Senile Dementia and Related Disorders,* edited by R. Katzman, R. D. Terry, and K. L. Bick, pp. 5–9. Raven Press, New York.
4. Gruenberg, E. M. (1978): *Patterns of Disease Among the Aged.* National Institute on Aging, Bethesda, Maryland (HEW Publication No. NIH 78-1410).
5. Katzman, R., Terry, R. D., and Bick, K. L. (eds.) (1978): *Aging, Vol. 7: Alzheimer's Disease: Senile Dementia and Related Disorders.* Raven Press, New York.
6. Scheff, S. W., Bernardo, L. S., and Cotman, C. W. (1978): Decrease in adrenergic axon sprouting in senescent rat. *Science,* 202:775–778.
7. A Task Force Sponsored by the National Institute on Aging. (1980): Senility reconsidered: Treatment possibilities for mental impairment in the elderly. *JAMA,* 244:259–263.
8. U.S. Senate Special Committee on Aging (1979): *Developments in Aging: 1978.* U.S. Government Printing Office, Washington, D.C.

ENCLOSURE # 2

Clinical Aspects of Alzheimer's Disease and Senile Dementia, (Aging, Vol. 15), edited by Nancy E. Miller and Gene D. Cohen. Raven Press, New York 1981.

Clinical Aspects of Alzheimer's Disease and Senile Dementia: Synopsis and Future Perspectives in Assessment, Treatment, and Service Delivery

Nancy E. Miller and Gene D. Cohen

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Senile dementia of the Alzheimer's type is a disorder of growing medical importance, and one of immense social and economic impact. It is a chronic, progressive, deteriorative neuropsychiatric brain disease accompanied by profound and devastating effects on memory, cognition, and ability for self care. Historically, senile dementia has been assumed to be an inevitable result of normal advancing chronological age. Current scientific trends, however, suggest that this serious and irreversible impairment of brain function represents an insidious disease process that is separate and distinct from normal aging: The majority of older persons do not develop this disorder within their lifespans, and it is estimated that only 5 to 7% of the population at age 65 have moderate to severe dementia of the Alzheimer's type. However, the incidence of Alzheimer's disease is strongly age-related, and the risk of developing this disorder increases as one grows older. Given the steadily rising proportion of the population that is elderly, and given conservative estimates that one out of every five Americans will be past 65 within the next half century, the public health implication and the social and economic impact of the problem is obvious and overwhelming.

This volume presents a practical, theoretical, and multidisciplinary approach to contemporary clinical knowledge in the assessment and treatment of Alzheimer's disease, senile dementia, and related conditions.

The scope of the volume ranges from a comprehensive focus on questions of nomenclature and differential diagnosis to an inquiry into intrapsychic, affective, and cognitive concomitants of the disorder. It includes analyses of the safety and efficacy of a variety of behavioral, pharmacologic, and other somatic treatment regimens, offers multiple perspectives on models of care and service delivery, and considers the emotional, social, and economic costs of developing this disease at the family, community, and societal levels.

The volume is written for those with an interest in any number of aspects

of the chronic dementing conditions of late life, with the expectation that an understanding of one's own area of expertise may be significantly enhanced by a fresh awareness of the multiple factors impinging on the care and well-being of the elderly individual with senile dementia of the Alzheimer's type.

The volume constitutes the second set of proceedings to emerge from a series of conferences on Alzheimer's disease and senile dementia, jointly sponsored by the National Institute of Mental Health, the National Institute on Aging, and the National Institute of Neurological and Communicative Disorders and Stroke. The initial publication, entitled *Alzheimer's Disease: Senile Dementia and Related Disorders* (Katzman, R., Terry, R. D. and Bick, K. L., eds., Raven Press, New York, 1978), which presents an extensive scientific overview of the field, focuses largely on basic etiological and pathophysiological studies of the dementing disorders of later life. The present volume, in contrast, tackles the clinically oriented problems of diagnosis and management, which in many respects are more difficult to study, in that they are less amenable to precision in scientific investigation, and must take into account not only factors on the molecular, cellular, and neurophysiological levels, but must also consider more molar aspects of the problem on the organismic and societal levels as well.

As the initial volume suggests, considerable progress has been made over the course of the past decade in delineating new etiological models of dementia and in studying possible metabolic, neurochemical, genetic, immunological, and viral abberations associated with dementing conditions of later life. Yet, as the contents of this volume reveal, although much has been learned, the extent of our ignorance is still staggering, and current challenges to clinical investigators could not be more stimulating or provocative.

In the process of reviewing the chapters included in this volume, which were prepared by authors representing widely divergent theoretical perspectives and differing experimental approaches to clinical knowledge, a number of themes or consistently expressed problems began to repeatedly manifest themselves with significant consistency and clarity. Because in many instances these concerns appear so obvious, basic, and deceptively simple, they are especially prone to neglect by the serious investigator. Yet, many of these items constitute important variables, which are often difficult to address empirically because they represent a complex series of confounded factors, frought with methodological pitfalls and colored in many instances by emotional preconceptions and closely cherished beliefs. In the course of briefly reviewing the major issues addressed in this volume, these special themes will be highlighted and described.

A number of these themes present themselves at the most basic clinical levels of knowledge. For example, serious questions continue to be raised regarding nomenclature and how this disease, or spectrum of diseases, should be classified—what it should be called, and what the nature of the clinical criteria should be for positive identification of the disorder in the living patient. Since there is no chemical, radiologic, or psychometric examination or indicator that is specific for Alzheimer's disease, the diagnosis can only be reliably made postmor-

tem on the basis of histopathologic data or clinically by a process of excluding potentially treatable dementias. Accordingly, reliable data regarding the prevalence of the disorder are difficult to obtain, and much of the reported literature is problematic because of great variability in the methods of classification and diagnostic procedures used in identifying the disorder. Almost without exception, both authors and discussants in this book underscore and reiterate the serious difficulties that accrue in research as the result of the lack of a uniform, well-defined nosology for classifying the dementias of later life.

The opening chapters review this problem in detail. Zbigniew J. Liposki provides a historical perspective on the language of psychopathology related to brain disorders and describes the ambiguous and overlapping terminology that has been used to characterize these states in the past. He depicts the more rudimentary efforts to classify organic mental disorders that have taken place over the span of centuries, and brings us up to date with an analysis of the more recent development of the classification of mental disorders in American psychiatry. This includes conceptualizations used in the American Psychiatric Association's second edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-II) published in 1968, and continues through the significantly revised and recently published third edition of this manual, DSM-III. The chapter broadly discusses the place of senile dementia and Alzheimer's disease in the context of, and in relation to, other organic mental disorders, and describes the distinctions specified in DSM-III among classifications of delirium, dementia, amnestic syndromes, organic hallucinosis, as well as among the organic delusional syndromes, organic affective syndromes, and organic personality disorders. Lipowski underscores a second theme that is also expressed repeatedly, from various theoretical perspectives, and across disciplines throughout this volume. This regards the critical importance of psychological and social factors as essential components coloring the manifestation of the illness and the fresh appreciation that symptomatology in all organic/mental disorders is multifactorial in origin.

In further delineating aspects of nomenclature, Paula Clayton and Ronald Martin focus on the historical development of the senile and vascular dementias as specific nosological entities, and outline the rationale in DSM-III for encompassing senile dementia of the Alzheimer's type under the classification of "primary degenerative dementia." They also describe the rationale for selection of the term "multi-infarct" dementia to describe stepwise deterioration of intellectual function in the face of focal neurological signs and a fluctuating course of disease. The current DSM-III classification has eliminated the distinction between "psychotic" and "nonpsychotic" aspects of organic mental disorder, and has incorporated the recognition that mental, neurologic, and pathologic findings appear to be indistinguishable in Alzheimer's disease regardless of whether onset is in the senium or the presenium. The DSM-III incorporates a new multiaxial approach to diagnosis, which yields a far more complex and comprehensive picture of the patient: In the context of this classification system,

the first axis reflects the primary disorder, the second includes personality description, the third lists associated medical disorders, the fourth indicates the presence of recent life stress, and the fifth describes highest level of adaptive ability in everyday life during the past year. The authors of both nomenclature papers were active members of the Section on Organic Brain Disorders in the Committee on Nomenclature and Statistics of the American Psychiatric Association, and they therefore can provide the reader with a bird's-eye view of the developing conceptualization and logic behind the most recent shifts in nosology descriptive of the organic mental disorders. The new classification has been clinically tested and has been reviewed, rewritten, and changed in response to criticisms and suggestions from the field. Only far more extensive use over time, however, will confirm the validity and utility of these new adjustments.

It is clear that different nosological schemes often reflect different aims of classification and different unstated assumptions underlying their purpose and development, and that such classifications may manifest different strengths and weaknesses, depending on the context in which they are used. In keeping with this, the lively discussion following these papers highlights two somewhat divergent approaches to nomenclature, the more circumscribed and phenomenological approach to classification of organic mental disorders, as exemplified in the 9th edition of the *International Classification of Diseases*, ICD-9, as formulated by the World Health Organization, and the broader, operationally descriptive American view as exemplified in DSM-III. The discussants from Great Britain cogently note, for example, that although the International classification (ICD-9) ranks dementing states by operationally defined grades of severity, the DSM-III has not incorporated a formalized system for indicating severity in its classification of organic mental disorders. Some degree of discomfort is also expressed regarding the new American system of labeling symptomatic affective and schizophreniform psychoses, occurring concomitantly with organic states, as "organic affective syndromes," "organic personality syndromes," or "organic delusional syndromes." The British contend that such a nosological schema fosters the unproven assumption that it is the underlying organic states themselves that are both necessary and sufficient causes for manifestation of the concomitant behavioral symptomatology. It is their view that since the causal association between these is unknown, and the clinician may simply be dealing with the conjunction of two relatively discrete and independent groups of phenomena, it would do well to describe these states on the basis of further empirical research rather than deciding them at the outset by "arbitrary" diagnostic rules. However, views on this point differ, and although some worry that widening the scope of definition of the psychoorganic syndromes may result in the blurring of conceptual parameters of diagnosis, others feel that, on the contrary, by including diagnoses such as hallucinosis, organic delusional syndrome, organic affective disorders, and organic personality disorders, fresh research on the borderland of disorders spanning the range between organic and functional psychopathology will be significantly enhanced. It is hoped that the new classification will stimulate

the formulation of testable hypotheses, loosen entrenched conceptions about organicity, and encourage a fresh look at these unresolved issues. Such lively controversy is likely to remain in this area for some time to come, and represents a healthy indication that scientists continue to ponder and struggle with complex questions of classifying behavioral symptomatology in the face of definitive brain disease. If the new formulation advanced in DSM-III serves to provoke more discussion, fresh conceptualization, and the uncovering of new etiologic clues, the result is likely to be a rapidly advancing field, a more secure knowledge base, and a richer understanding of the nature and possible treatment of these multifactorial brain disorders.

That the situation grows increasingly complex is indicated in the following chapter on "The Borderlands of Dementia." Here, Barry Gurland suggests that not only do serious questions remain regarding the optimal methods to be used in classifying the brain disorders of later life, but also that even more basic are those questions pertaining to the nature of the actual criteria used in identifying the presence of senile brain disease of the Alzheimer's type. Depending on the manner in which the diagnosis is formulated, the effect of socio-cultural variables on rates of disease appear to differ. A number of studies undertaken in both the United States and Great Britain, for example, suggest that when dementia is measured by psychological indicators such as mental status questionnaires or rating scales, rates and severity of dementia appear to vary with socio-cultural factors. On the other hand, the association between dementia and social class appears to be weaker when diagnosis formulated by a clinician is the indicator, rather than when a psychological instrument acts in this capacity. This discrepancy raises the specter of the differential validity of various techniques commonly employed in the assessment of brain disorder in older persons. Much remains to be learned about precisely what it is that is being measured in each type of evaluation, and what the systematic effects are of the numerous intervening variables that color expression of symptoms and manifest behavior. Since biologic or behavioral markers pathognomic of the disease have not yet been found, there is as yet no real agreement regarding the most favorable approach to positive identification of the disease. Results from empirical studies continue to be inconsistent, and it remains unclear whether clinical diagnosis, say in the hands of a psychiatrist or neurologist, is more reliable than other techniques, such as tests and rating scales, for the classification of dementing psychopathology. Accordingly, many of the significant discrepancies in prevalence rates of dementia reported in different community surveys may be partially due to differences in the methods and criteria used for diagnoses. Furthermore, there may be an overabundance of brains in the advanced stages of dementia that come to autopsy, as well as a social class bias in the collection of brain tissue, such that sociocultural differences in prevalence could easily be missed in those studies based only on postmortem examinations.

Gurland also raises fundamental issues regarding the whole nature of the brain-behavior relationship in dementia. He notes that although severity of cogni-

tive deficit is typically correlated with severity of changes in the neurophysiological substrate, there appear to be many exceptions to this rule, with some subjects showing gross brain pathology but minimal performance decrements, and others showing mild structural changes in brain accompanied by massive behavioral incompetence. It is not clear to what extent performance on mental status examinations is influenced by both dementia and sociocultural characteristics, and whether the relationship between test performance and brain deterioration in the dementing process is more common in certain sociocultural groups. These issues arouse continuing controversy regarding the relationship between structure and function, between the nature, degree, and extent of damage to the neurophysiologic substrate and the resulting variety and severity of manifest cognitive and behavioral deficit. They raise questions regarding the functional plasticity and modifiability of neural systems, the role of nature and nurture, the effects of learning, of cortical redundancy, and of the reserve capacity of the brain.

Gurland speculates about mechanisms that may underlie an association between cortical reserve capacity, brain insults, sociocultural characteristics, and prevalence rates of a dementing process, and suggests that premorbid personal, intellectual, and adaptive factors may have a profound influence on the behavioral sequelae associated with altered brain function in later life. Social class and education may, for example, be associated with the preservation of social skills and personal habits that enable the older person with dementia to survive in the community for far longer periods of time.

As the animated panel discussion following Gurland's paper suggests, current knowledge regarding the specificity of brain-behavior relations in dementing conditions and the role of auxiliary sociocultural variables and character traits remains an open question. As such, it constitutes a critically important research challenge for the future.

H. S. Wang, in "Neuropsychiatric Procedures for the Assesment of Alzheimer's Disease," underscores the view of both Drs. Gurland and Lipowski in suggesting that Alzheimer's disease is a complicated disorder that is influenced by a broad variety of physical, psychological, and social factors. In the course of formulating a diagnosis and establishing a treatment plan during the neuropsychiatric evaluation, Wang suggests that it is important to take many different levels of function into account. The evaluation should include measures of memory and cognition, assessment of functional and structural brain impairment, a review of behavioral manifestations affecting the individual's capacity for self-care, as well as quality of the patient's interpersonal relations and ajustment. In keeping with former authors, Wang stresses that often there is not a one-to-one correlation between brain impairment, behavioral or affective dysfunction, and capacity for self-care, such that many levels of analysis are necessary in order for a comprehensive, realistic treatment appraisal to be formulated.

The chapter reviews the validity, efficacy, and comparative cost of neuropsychiatric measures and procedures currently available for evaluation of various aspects of Alzheimer's disease, including an overview of relevant history taking,

and the psychiatric and neurological examination. A concise description of the efficacy of various laboratory procedures is provided, including plain skull X-ray films, pneumoencephalography, cerebral angiography, radioisotope brain scans, cisternography, electroencephalography, cerebral blood flow, brain biopsy, computerized axial tomography, and positron emission transverse tomography.

In the following paper, Edgar Miller considers the goals of psychological assessment in Alzheimer's disease, which include the measurement of cognitive and perceptual change from premorbid levels, the formulation of a differential diagnosis, and the rendering of decisions about management and placement. In his report, Miller considers each of these subjects in turn, reviewing what is known on a systematic basis and highlighting areas in need of further work.

Since the success of any systematic study of dementing conditions depends most importantly on the reliability or accuracy of the formulated diagnoses, Miller approaches the recurrent problem of differential diagnosis from a rigorously empirical perspective, asking methodological questions that few clinical investigators working in the field have taken seriously into account. The chapter addresses basic issues concerning diagnostic validity, problems relating to direct and indirect contamination effects, questions regarding the homogeneity of subject samples, shifts in base rates of disease, and how and where cutoff points should be set in order to optimize overall levels of correct classification. For example, it is clear that opinions and value judgments often enter the classification process in unspecified ways, and that differential costs and benefits accrue, depending on the nature of the goal to be ascertained. Thus, as Miller states, "It could be argued that since depression is a treatable condition, it is a much more serious error to misdiagnose a depressed patient as demented, than the reverse. Would you set the cutoff score to minimize this type of error, even at the expense of a greater risk of falsely classifying a dement as depressed?"

In addition to questioning the adequacy of test norms for assessing the elderly, and especially the effects of changes in cohort characteristics over time on age-rated normative data, the author also underscores the great need for cross-validation in assessment research, as well as the need for more and better multiple test forms in order to control for practice effects.

In addition, the chapter reviews the utility of a wide variety of psychometric instruments including tests of IQ, memory, verbal learning, design copying, language, and orientation, as well as traditional neuropsychological measures, rating scales, and mental status examinations. Automated procedures, such as matching to sample techniques and the use of direct observational methods, are also discussed.

Although psychological tests are often quite useful in determining differential diagnoses, they generally are less successful in measuring cognitive decline from premorbid levels. Only rarely is reliable premorbid information available to the clinician, and even when factors such as education and occupation are controlled for, it is suggested that there is still considerable fluctuation in intelligence levels within categories. Moreover, in many instances, even if differences are

found at a group level, it is not always possible to reliably and accurately interpret data obtained from the individual case.

These methodological parameters are more fully considered in the following report on the "Nature of the Cognitive Deficit in Dementia." Here the author is not so much concerned with issues facing the clinician in the diagnostic setting as with providing a comprehensive synopsis of the experimental research literature on the nature of cognitive and perceptual impairment in demential disorders. Since dementia is associated with diffuse and wide ranging pathological changes in the brain, it is not surprising that a broad spectrum of functional and behavioral deficits has been identified by experimental investigators. Since so many behavioral capacities are eroded by senile dementia of the Alzheimer's type, Miller emphasizes the need not only for more descriptive research but also for research based on explanatory theoretical models, which can be confined to a single behavioral system. In the area of cognitive research especially, there have been few systematic attempts to explain a particular problem in depth. Rather, the knowledge base is meager, with many of the areas studied representing fragmented efforts, which have not built on findings reported by others. The need, therefore, is great for investigators to make sustained career commitments to research in this area. Many experimental studies of cognition in dementia suffer from major methodological flaws, especially stemming from problems in the selection of subjects. Again, the theme is reiterated that study samples are poorly described, that criteria used in selection vary markedly, and that results, accordingly, are often noncomparable and inconsistent.

Miller discusses what is known about cognition in dementia, and presents the available evidence regarding distractibility, disturbances of attention, utilization of acoustic coding in short-term memory, performance on tests of iconic memory, long-term storage, free recall, memory for remote events, acquisition and retrieval, etc., but concludes that, overall, many aspects of intellectual function memory in dementia remain unexplored. In addition, although senile dementia of the Alzheimer's type is a slowly progressive disease, there are no empirical reports in the literature following the development of cognitive impairment across different stages of the course of disease. Moreover, there have been extremely few studies of such functions as perception, information processing, visuospatial abilities, and thinking in dementia. For example, although clinical impression suggests that there appears to be an increased incidence of sensory impairment in dementia, both visual and auditory abnormalities have been minimally investigated. Similarly, although some reports indicate that naming difficulties in senile dementia of the Alzheimer's type differ from those occurring in more usual types of dysphasia, there have been few investigations of narrative speech in this disorder. Rather than simply exploring the presence or absence of a particular deficit, however, Miller advises investigators to attempt to approach experimental research in this area from a clinical management perspective. Given that the etiological factors in this disorder remain unknown, the predominant problem presented by the patient with dementia is one of manage-

ment—that is, how can the clinician diminish the importance of cognitive deterioration and ensure that the individual retains his functional capacities for as long as possible? Accordingly, the experimental question then shifts from trying to define the deficits to attempting to establish under what circumstances these are either maximized or minimized. For example, how well do older patients with dementia retain information under different conditions of acquisition?

Some innovative and beginning approaches to these questions are explored in the following section, which focuses on somatic, behavioral, and environmental treatment and management parameters in the dementing states of later life. Although many of the attributes and subtleties of the cognitive impairment accompanying dementia remain to be systematically described, on a gross and descriptive level, the clinical hallmark of dementia consists of symptoms of progressive deterioration of intellect and memory. In keeping with Edgar Miller's suggestion regarding investigations that attempt to establish under what conditions the severity of dementia impairment can be ameliorated or minimized, there have been a host of studies undertaken that have made the attempt to identify a chemical agent capable of reducing, halting, or reversing the intellectual decline associated with dementia.

In the following chapters, Drs. Funkenstein, Hicks, Dysken, and Davis review the substantial literature on the major classes of drugs that have been used in an effort to improve cognitive function in elderly patients. Some of the agents touched on in this chapter include classes of cerebral vasodilators, central nervous system stimulants, anabolic substances, RNA-like compounds, anticoagulants, vitamins, chelating agents, and cholinomimetic substances. After reviewing the available evidence, the authors conclude that although no drug has demonstrated any clear degree of efficacy in reversing the cognitive failure of dementia, some of the drugs reported on may be useful in certain types of patients. In many of the studies, however, reports of improvements may actually be secondary to changes in mood state rather than a result of enhanced cognitive function. Pharmacological research on the dementias of later life is no less affected by methodological pitfalls than are other substantive research areas. Such studies, for example, often exhibit a lack of precision in describing the character of the experimental sample and the nature of the outcome measures used. In addition, in many of the drug studies, terms used to describe beneficial outcomes often indicate an affective rather than a cognitive locus of action, with the investigators stating in their conclusions that the patients are "brighter," "less irritable," or "more socializable," etc. Investigators often fail to separate gains due to mood enhancement from primary effects on intellectual function, and do not use psychometric instruments capable of reliably measuring cognition. Moreover, few of these studies actually control for the effects of medication on affective status and motivation levels. Research in this area is progressing rapidly, however, and many promising leads are still in the experimental stages of development.

Although truly effective pharmacologic treatments for intellectual deteriora-

tion in dementia have not yet been formulated, significantly greater success has been achieved in ameliorating those psychopathologic affective states that are often seen to develop concomitantly with dementing processes in later life.

Often, the affective and interpersonal symptoms accompanying senile dementia such as depression, anxiety, agitation, irritability, withdrawal, paranoia, etc. can accelerate deterioration. Yet, as Fann and Wheles reveal in their chapter, many of the symptoms of these concomitant conditions are treatable, and adaptive behavior is generally seen to improve when the affective symptoms are effectively identified and managed. This chapter yields practical suggestions for pharmacological management of the affective components of senile dementia, and reviews relevant studies of drug trials with antipsychotics, anxiolytics, anticoagulants, MAO-inhibitors, ergot alkaloids, vasodilators, central nervous system stimulants, cholinergic agents, hormones, enzymes, vitamins, nootropic drugs, etc. The studies reviewed vary significantly in their degree of methodological rigor, ranging from open studies with no placebo control groups, to double-blind, placebo-controlled, crossover designs. Even in the latter studies, however, many of the reports manifest methodological shortcomings, which continue to make it difficult to assess the accuracy of their contributions. The frequent presence, for example, of simultaneous physical and psychiatric disorder in older demented persons and the consequent effects of polypharmacy often make it difficult to differentiate the intended effects of the experimental drug from side effects, placebo effects, etc. Furthermore, in various of the studies of anti-anxiety, antidepressant, and antipsychotic agents, the homogeneity of the experimental group is not always assured, and oftentimes, deteriorated subjects at the endpoint of dementia are used for study. Furthermore, sample sizes are frequently too small and the trial period for the experimental agent is often too short. On the whole, however, the authors conclude that enough reliable evidence is available to suggest that much can be done to ameliorate coexistent anxiety, depression, agitation, and paranoia, and that when used appropriately, psychopharmacological treatment can significantly relieve emotional distress in the dementing conditions of later life.

Both the authors and the panel discussants highlight the fact that because older persons have reduced tolerance to psychotropic medication, they require lower doses to reach a desired therapeutic effect. Older patients may manifest frequent and severe side effects at essentially therapeutic doses. Side effects include drug-induced Parkinsonism, tardive dyskinesia, for example, or the exacerbation of psychotic symptoms associated with anticholinergic toxicity. There appears to be reliable consensus among both researchers and clinicians regarding recommendations to limit the use of agents with potent anticholinergic side effects in older persons. In treating depression, for example, the use of antidepressants that have minimal anticholinergic activity is strongly advised, and it is suggested that agents such as the monoamine oxidase inhibitors be given greater consideration with this population than they have had in the past. Not much evidence from double-blind studies is available regarding the differential effects of antipsychotics and antidepressants in elderly persons with dementia, and

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the question of using electroconvulsive therapy (ECT) in the management of the affectively depressed older person with organic brain disease has been even less adequately explored. It is speculated that ECT may be an extremely effective method for the treatment of depression in cases of senile dementia, but further studies are urgently needed. Fuller consideration of specific practical issues such as the somatic treatment of choice in cases with mixed symptomatology, the nature of drug side effects in the elderly, specific contraindications, dosage schedules, drug-interaction effects, and problems resulting from longer term trials of medication can all be found in the discussion sections following each of the chapters on somatic approaches to treatment.

The question of affective response to illness is explored from a different perspective in Adrian Verwoerdt's innovative chapter on the use of individual psychotherapy with senile dementia patients. This chapter was specifically invited in an effort to counter the strong sense of nihilism so often manifested by clinicians and staff about older persons with brain disorder. Such attitudes are often, at least partially, the result of the staff's own feelings of helplessness and despair, which often stem from unrealistic expectations and goals. Although intellectual function and capacity for self-care may be severely limited in older persons with Alzheimer's disease, the capacity for affective responsivity is often preserved until the end stages of disease.

Verwoerdt suggests that a psychodynamic approach to treatment of the demented patient is both feasible and appropriate when incorporated as an integral part of a comprehensive treatment plan. Such an approach can serve to deepen the clinician's understanding of the conflicting emotions, fears, and intrapsychic mechanisms that color the patient's subjective world, that substantially affect his adaptation to neuronal impairment, and that impinge on the therapist's own subjective motivation to become involved on a sustained basis in the treatment process. The chapter is rich in clinical examples and filled with a wealth of practical information regarding treatment on the clinical level. It is based on the recognition that no matter what symptoms the patient presents, there is always something the practitioner can do to give relief. The aim of treatment, which the author suggests must be continued indefinitely throughout the course of the disease, is to facilitate optimal functioning as long as possible, by maintaining and utilizing residual skills, enhancing mastery and adaptive coping, and by relieving concomitant emotional distress. Verwoerdt reiterates the importance, stressed throughout this volume, of adopting a patient approach to long-term management, rather than treating the individual with expectations derived from a short-term, acute approach to care.

The chapter describes a variety of psychological defensive techniques aimed at mastery and control, at conservation of energy, and at retreat from threat, which are commonly manifested by elderly patients with brain impairment. The behavioral patterns commonly associated with these techniques, and the implications of these for the individual's adjustment and clinical management, are presented.

The chapter also traces common obstacles to the therapist-patient relationship

and describes the dementia patient's penchant for primary process thinking, his impaired capacity for abstraction, and his common use of paleologic thought, analogies, displacement, and condensation. As a result of these deficits in cognition, Verwoerdt suggests that the use of a nondirective interviewing style is contraindicated with dementia patients. Instead, an approach providing the patient with consistency, predictability, cognitive structure, and the opportunity for closure is substantially more useful.

Patients with Alzheimer's dementia often present with acute traumatic anxiety and/or with feelings of depletion, abandonment, helplessness, and shame. Depressive loneliness is extremely common in these individuals, and as Fann and Wheles note, tends to exacerbate the severity of symptomatology. The author describes the practical management of a variety of defensive operations and discusses various clinical approaches to problems of combativeness, apathetic withdrawal, paranoia, mania, hypochondriasis, dependency, regression, etc. Although the goal of treatment is aimed at reducing helplessness and encouraging a sense of self-control, Verwoerdt poignantly and aptly reminds us that "self-care has appeal only to the extent that there is something to live for."

This chapter speaks knowledgeably about those emotional phenomena and personality changes that, although difficult to classify and quantify, appear to exert a powerful effect on the expression of behavior in persons with progressive senescent brain impairment. Although systematic research in this area has been sparse, every clinician working on the front lines with demented patients is aware of their presence and in some way must come to terms with them. As the discussion section following the chapters on nomenclature indicates, consensus is far from unanimous in regard to how these symptoms should best be classified. Whether the associated symptoms of dementia are described from a psychoanalytic perspective, or from a behavioral framework, whether or not one assumes that a close correspondence exists between brain structure and specificity of behavioral impairment, whether the symptoms are classified as integral parts of the organic spectrum of disease, or as independent syndromes, their presence needs to be acknowledged and understood, carefully diagnosed, and appropriately treated. At this point there is little to indicate, on an empirical basis, the parameters of these affective symptoms or syndromes, their frequency of occurrence, their differential responsiveness to various treatment modalities, or their long-term prognostic significance. It is evident that much difficult work remains to be done.

The need for more research is also emphasized in the chapter on behavioral therapies by Carl Eisdorfer, Donna Cohen, and Carolyn Preston. The authors reinforce previously reiterated views, suggesting that behavior is multidetermined, that therapeutic nihilism is deleterious, and that much of the literature examining efficacy of treatment strategies continues to focus on acute methods of curative treatment, rather than on the management and maintenance of function in chronic disease.

Eisdorfer et al. focus on what is known about a broad variety of treatment approaches with elderly persons with dementia, which include different operant

techniques, cognitive interventions, and psychosocial treatments. The efficacy of efforts to change a variety of maladaptive behaviors such as muteness or screaming, for example, or bowel and bladder incontinence, poor personal hygiene, obsessional rituals, self-injurious behavior, etc. are explored, and techniques to increase social interaction, enhance cognitive skills, improve ability for self-care, and prevent deterioration are also presented. Included among these approaches are techniques such as reality orientation, remotivation, resocialization, activity therapy, and group, milieu, and family therapies.

Questions concerning the effects of relocation stress, and the fostering of dependency and learned helplessness are taken into account, as are descriptions of covert treatment goals, such as staff assumptions regarding the importance of "conforming" behavior on the part of the patient. The chapter reviews a broad scope of treatment literature and contains descriptions of practical and successful approaches to problems in patient care. It also highlights the minimal amount of outcome research that has been done in this area.

These sentiments are echoed by M. Powell Lawton in his description of the ecological context in which persons with dementia live. Lawton suggests that as an individual's base of behavioral competence erodes, the effect of the environment assumes increasing importance in determining well-being.

He hypothesizes that although brain-impaired aged are more vulnerable to noxious environments, on the other hand, small environmental improvements may produce disproportionate effects in "low competent" individuals. Accordingly, to the extent that the environment surrounding the demented individual is either deprived or stressful, behavior and affective outcomes will be more negative than necessary. Behavioral mapping of the daily activities of demented elderly persons in institutionalized settings reveals a low diversity of spatial experience, significant impoverishment of social behavior, and high frequencies of isolated and passive activity, such as sleeping or sitting.

Since the institutional milieu of demented patients verges on sensory deprivation, Lawton suggests that it would be useful to emphasize diversity within the circumscribed treatment area, and to attempt to produce greater variation in the types of behavior demanded of individuals with dementia. On the other hand, Lawton notes that despite the intention that treatment-environment improvements should enhance or increase sensory stimulation, orientation, self-maintenance, and social behavior, only limited empirical evidence is available to suggest that any of these aids are, in fact, effective. Edgar Miller's remark—in the chapter on the nature of the cognitive deficit—indicated that there exist apparent perceptual abnormalities in individuals with dementia, but that little is known about these; similarly, more needs to be evaluated regarding the effects of sensory deprivation and sensory overload, stimulus complexity, and novel experience on demented patients. Although it is often asserted that persons of lower cognitive competence require simpler environmental stimulus fields, if adaptive behavior is to result, again, there is little systematic evidence on this point.

As Gurland, Miller, Verwoerdt, Eisdorfer, and Lawton have all suggested,

more needs to be known about the possibility of modifying behavior, and the available plasticity of response in these patients. Moverover, if demented persons do manifest an improvement in behavioral activity as the result of a specific environmental intervention, what are the implications of this for management, housing, and approaches to institutional care? Should those with senile dementia, for example, be clustered in a single location, or housed in areas where fully mentally competent persons reside? Lawton suggests that the literature is equivocal on this point, and notes that although some studies suggest the importance to demented patients of the presence of mentally competent persons, if social interaction is to take place at all, oftentimes strong objections to this are raised by both relatives and staff.

In addition to questions regarding how the progressive chronic brain disorders of later life are to be classified, diagnosed, treated, and managed, there is a real need to better understand how effectively, in what contexts and settings, and at what cost these clinical and social services are delivered to patients and their families.

In their chapter on community treatment for aged persons with altered brain function, Robert L. Kahn and Sheldon F. Tobin provide a historical perspective regarding the effectiveness of mental health models for treating older persons with altered brain function in their own community. They suggest that the provision of community mental health services to the aged has declined precipitously and consistently since the end of World War II, such that, at present, most community service programs have policies of screening out older persons with Alzheimer's disease and senile dementia. With the pressures toward deinstitutionalization, the emptying of state mental hospitals, the failure of community mental health centers to treat major mental disorders of the aged, and the effects of recent health care legislation, there has emerged a "new custodialism," exemplified by the accumulation of masses of older persons with brain disorders in nursing homes. With few exceptions, services for the elderly in the community today remain fragmented and uncoordinated, with limited integration between psychiatric, medical, and social service networks.

Outside of the nursing home, the focus is not on long-term assistance in helping to maintain chronically ill patients in their natural communities so much as on expensive, technology-intensive care, oriented toward treatment of acute medical illness. The authors cogently describe the deleterious effects of custodialism, and of the provision of overintensive, overprotective services on the functional capacity of the elderly patient with brain impairment. They note that such individuals commonly develop what is described as "excess disability," in that they manifest greater functional disability than warranted by their health status. As a result of institutionalization, a "social breakdown syndrome" occurs, in which the individual is torn from his or her moorings in the community, and added impairment is superimposed on that due to intrinsic properties of the pathology. Once social supports collapse, as when the old person is admitted to an institution for a prolonged period, they are often difficult to reconstruct.

In order to circumvent this, a series of basic principles of community mental health care of the aged is delineated, which includes an emphasis on (a) early identification and prompt treatment, and a focus on minimal dislocation by providing home evaluation and treatment in the community, if possible, and strictly time-limited hospitalization, close to home, if not; (b) building a relationship of trust and commitment with a community catchment area by providing integrated service alternatives, which include such services as assessment units, home care, day care programs, holiday relief for families, time-limited hospitalization and continuity of care—such that the same personnel are responsible for the patient in different settings and times, etc. A number of progressive and effective European and American models of community care are described that have successfully integrated these principles of minimal intervention.

When interpreting findings from the literature in this area, it is often useful to note the manner in which results are colored by particular value judgments and unspecified covert assumptions. In some studies, for example, presumably benign outcomes are limited to relatively trivial criteria of effectiveness. Additionally, therapeutic strategies often do not distinguish primary pathological behavior patterns from those patterns arising as a result of institutionalization itself. Moreover, as noted by Eisdorfer et al., there is often confusion in distinguishing between basic goals, such as the slowing of intellectual deterioration in the patient, and more limited goals, such as the value of having compliant patients, who cause few management problems for the staff. In many instances, the achievement of the latter may contradict the attainment of the former. Investigators often fail to acknowledge that very difficult and complex calculations of value, of costs and benefits, need to be made in these situations, and that sometimes the best solution for the family member may not constitute the best solution for the patient. Often, for example, relief to relatives and the best interests of the patient do not coincide. A delicate balance must be struck between providing for community care that fosters survival of the older person in the community for long periods and one that, at the same time, does not strain community tolerance and the family burden. The authors indicate that institutional care, by itself, can be either custodial, with negative effects, or therapeutic, by being brief and time-limited.

Elaine Brody presents a contrasting perspective regarding the value of long-term care institutions, noting that for many persons with brain dysfunction, these provide an important, appropriate, and necessary component of care. She skillfully describes how the current climate favoring deinstitutionalization places community care for institutions in a false position of competition, rather than of mutual and interactive support. She notes the need for community care services to be expanded enormously, and concomitantly, the need for "deinstitutionalizing" the institution.

The chapter exhaustively reviews the legislative and economic factors giving impetus to the growth of institutional facilities on the United States over the past 30 years, and lists the rates of institutionalization of the over-65 population

in different countries. Although data specifically focused on long-term care rates of Alzheimer's disease are inadequate, it is estimated that the current 5% figure in the United States—as a proportion of the institutionalized aged—represents a serious underestimate.

In line with the theme repeated by Eisdorfer, by Verwoerdt, by Fann, Kahn, Miller, etc., Brody also indicates that an acute care model has been imposed inappropriately on long-term care. She stresses the importance and desirability of a social-health model to replace a model based on acute and episodic care. Brody notes that risks of being admitted to an institution are multiply determined, and are significantly related to age, sex, race, and health status, such that individuals most likely to be institutionalized are over 80, white, female, and preponderantly from lower socioeconomic groups. Although the primary precipitant to institutionalization is poor health, the critical factor as to who is institutionalized involves the availability of adequate social support systems, especially family. Although at present fewer institutionalized persons are married and have children than age-matched controls living in the community, this situation may alter significantly, concomitant with the shifts in demography, social values, and life styles that are taking place in America today. In years to come, a clearly increasing burden of care will be placed on the institution and formal support system as a result of the rapid growth of the very old, and of those individuals at highest risk for dementia and institutionalization. In addition, as a result of women's changing life styles, their substantial increase in labor force participation will make them less available to give the overwhelming preponderance of home health services that they provide at present. Moreover, given the continuation of present trends of high rates of divorce and remarriage, complex and multiple, and often strained, filial loyalties may ensue.

Finally, the specter of people in advanced old age being cared for by aging children who have their own age-related problems, chronic disabilities, interpersonal losses, retirement, and lowered income to face is growing more common.

Senile dementia is one of the most socially disruptive diseases, placing severe burden on family members who, in most cases, have little recourse from community services. The burden on the family in terms of emotional strain, interference with employment and daily life, the effects on children, etc. is considerable. Accordingly, there is a significant need to reassess the whole question of burden, and the differential response to it, on the part of available health and social services.

In reference to this, the discussion section highlights the new and rapidly emerging community phenomenon of Alzheimer self-help groups, with information describing the origin and development of these local support networks into a national organization. These groups emerged partially as an answer to the extraordinarily stressful and complex effects an individual with Alzheimer's disease has on his own family members, with spouses often traveling in desperation from one medical center to another, searching for a cure or for definite answers, and refusing to institutionalize the patient. With the advent of these

groups, physicians diagnosing the disorder now have a place to direct the family that will assist them in their emotional adjustment, ease the stress of living with chronic illness, and supply behavioral methods to spouses and relatives to assist them in maintaining the patient at home. The rapid development of these groups indicates the presence of a profound need on the part of relatives and family members, and accentuates the importance of involving the patient's family in the formulation and development of a realistic treatment plan.

Ray Valle's chapter looks into these issues one step further, describing what is known about natural support systems, not only generally, but also specifically, as they are differentially constituted in different sociocultural and ethnic groups. In the decades to come, partially as a result of improved life expectancy, there will be far greater numbers of minority elderly, yet there continues to be a serious dearth of information regarding the prevalence of dementia in these groups. Little is known regarding the role ethnocultural factors play, for example, in determining the expression of symptomatology and patterns of coping in the dementing illnesses of later life. Valle suggests that various minority groups experience greater exposure to high-risk occupations and toxic substances, and speculates that different subcultures may have different dietary habits or immune system deficits that could affect the development of illness or the nature of the symptom picture in dementia. Minority groups typically occupy the lowest rung of the economic ladder, manifest lower life expectancies and higher morbidity rates, and are more vulnerable to developing such conditions as diabetes, hypertension, lung disease, and heart disease than are individuals in the majority culture. Accordingly, these ethnic and cultural groups are placed in "multiple jeopardy," often presenting to the physician at more advanced and severe stages of disease, while at the same time underutilizing available health resources. Valle outlines the different forms of natural support networks that constitute endogenous caregiving systems, and suggests that clinicians and community-based systems of care often fail to adequately take the strengths and contributions of these family supports into account. He underscores the very great need for reliable data on variables relating to altered brain function in later life as manifested in different sociocultural, racial, and ethnic groups.

In summing up these multiple trends for the volume, and looking toward the future, Odin W. Anderson, in the concluding chapter, questions the benign assumption that the solutions to formulating and implementing public policy in the area of senile dementia will soon become self-evident. Anderson wonders, given the demographics of the situation, and the ponderous behavioral problems regarding self-care, "whether we as a society will be capable of managing the increasing pressure of the sick aged gracefully." In agreement with Brody, Anderson notes that the nuclear family is geared not to the home but to the work-a-day world, and, as more and more women are employed, the social system and the family unit are becoming seriously overloaded. All data, he suggests, point in the same direction, that of facing exceedingly difficult answers in the years to come. Anderson echoes again what others have reiterated in previous

chapters: Health legislation has not been developed to optimally benefit the demented elderly. Medicare, for example, was designed primarily for short-term, acute episodes of illness, but long-term chronic illnesses constitute not an episode, but a way of life until death, with a constant and increasing drain on health resources. Although institutional care accounts for about 70% of all personal health services for the aged, little is known empirically about the cost of home care services, and knowledge of the interrelationships between family structures, delivery of home services, and care of the demented is exceedingly meager. Senile dementia is a disease process that places an enormous strain on the family, that often arouses nihilistic expectations and approaches to treatment on the part of the helping services, and one that is often obscured in the political process. Anderson bemoans the erosion of the ethic of service and duty, and espouses an emphasis on peace and comfort, and the shifting of attitudes toward chronic, rather than acute, models of care. He cautions, however, that there are no neat, social engineering solutions and reminds us, as Kahn and Tobin did so eloquently before, that all social objectives demand tradeoffs.

Although this overview touches on some of the highlights of the chapters to come, it can in no way convey the richness, detail, and complexity of the papers themselves. Each one of them is well worth reading in its entirety.

The volume reveals the complexities and the tragic effects of this disorder on patients, on their families, and on the community at large, on the one hand, yet amply spells out multiple areas in which substantial opportunities for innovation and discovery in research exist. It is our hope that in coming decades many of these questions will be answered by systematic research, if not for our parents' sake, then for our own and our children's sake. The chapters, as a group, suggest that a unitary model of illness and treatment is insufficient, that multiple perspectives on different levels are necessary, ranging from understanding at the molecular and cellular level, to consideration of the human organism in its entirety, including assessment of the nature, intrapsychic dynamics, premorbid intelligence, and sociocultural variables, as well as the patient's interface with family and society.

A variety of themes and concerns specific to the clinician weave their way through the chapters of this volume, reiterating over and over again such matters as the continuing controversy over the best method of classifying Alzheimer's disease and related disorders, distress over the high rates of error and lack of precision in characterizing current approaches to diagnosis, and the absence of reliable rates of disease incidence and prevalence in different geographic areas, social classes, and cultural groups. Also highlighted, and judged worthy of considerably closer scrutiny, is the broad spectrum of affective and behavioral symptoms that often accompany the core deterioration of intellect, and that, though typically overlooked, are in many instances responsive to appropriate treatment. In addition, considerable interest is focused on the role of premorbid character, on sociocultural, and educational variables as factors coloring the symptom picture, either by compensating for, or exacerbating, cognitive incapac-

ity; and related to this, of course, must be the continuing effort to better specify the relative closeness-of-fit in brain-behavior relationships in senile dementia of the Alzheimer's type. The nature of stage-specific changes in cognition, perception, and affect over the course of disease, and the compensating effects of sensory stimulation and environmental complexity on adaptation are also in need of further attention. Persistent themes on a more molar level involve questions regarding the differential social and economic costs of institutionalization versus maintenance in the community, the interface of service delivery structures with family networks, changing lifestyles and demographics on costs and patterns of care, and finally, the effects and ramifications of a basic shift in the philosophy of care delivery from acute intervention to chronic management.

The presence of the chapters in this volume suggest that important questions are being raised, that the field is at the threshold of developing a solid base of knowledge, and that interest in the dementias of late life—which has expanded so significantly in the course of the past decade—will continue, vigorous and unabated, for many years into the future.

ENCLOSURE # 3

Aging
Volume 7

Alzheimer's Disease: Senile Dementia and Related Disorders

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Aging
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Clinical Aspects of Alzheimer's Disease and Senile Dementia

Editors

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Preface

Over the past decade, as the elderly have become the fastest growing segment of the population, Alzheimer's disease/senile dementia has emerged as one of this country's major mental health problems. Current estimates suggest that there are approximately one million severely demented persons and another three million mildly to moderately demented persons in the United States. This illness has deleterious effects on cognition, personality, and affect, and empirical evidence also suggests that the length of survival of severely demented individuals is only one-third to one-half that of age-matched controls. Although the economic and emotional burdens of caring for patients with this late-onset brain disorder are great, there have been few systematic efforts to integrate findings from the scientific research literature to yield practical suggestions for direct approaches to clinical care. The aims of this volume are to highlight critical aspects of the theoretic and empirical literature relating to clinical assessment, treatment, and care of the patient with Alzheimer's disease/senile dementia; to translate these research findings, where possible, into direct indications for patient care; and to direct attention to areas of investigation with high potential for practical application and theoretical significance.

Our introductory chapter provides a synopsis of the significant themes and major substantive issues that appear throughout the volume and highlights the most promising directions for future research in the field. The volume is organizationally divided into three major sections. The first section consolidates what is known about the nosology, diagnosis, and behavioral correlates of Alzheimer's disease/senile dementia, with special reference to recent developments in the psychiatric nomenclature as documented in DSM-III and to the often puzzling association between sociocultural variables and manifest symptomatology. In this section, new advances and current practice in neurologic and psychiatric assessment are specified, useful psychometric evaluative procedures are described, and the nature of the cognitive deficit itself, as revealed in experimental studies of memory, perception, and information processing, is more clearly outlined.

The second section includes comprehensive reviews of the efficacy, safety, and reliability of the major treatment and management modalities in current use with elderly dementing patients. It includes an overview of pharmacologic and somatic agents used in treating the effects of cognitive impairment in Alzheimer's disease and a review of useful therapeutic approaches to its affective concomitants. The state-of-the-art in behavioral techniques, and psychodynamic approaches to management and understanding are discussed, together with the effect of the environment on care of the patient.

The concluding section describes the role of the service delivery system,

focusing on models of ambulatory care and community treatment as well as on innovative approaches to institutional care. In addition to formal institutional service delivery networks, the nature and value of the informal support network in helping to maintain the older person with dementia in the community is examined. The often neglected special difficulties associated with minority status are also addressed.

The final chapter reviews significant issues and trends in the formulation of social policy and public planning and assesses the economic and social impact of Alzheimer's disease/senile dementia on the fabric of American life.

The contributors represent internationally recognized authorities in the field and present new practical information, evaluate recent progress, highlight gaps in the structure of current knowledge, and outline high-yield areas for future research. The discussion sections interspersed throughout the text convey to the reader the sense of movement and excitement that characterizes this field today; they demonstrate the sense of hopefulness and lively controversy which is the mark of a newly developing system of scientific inquiry.

Although much remains to be learned about the cognitive pathologies of later life, they can no longer be regarded as invincible. This book comprises a rich and valuable resource for psychiatrists, neurologists, internists, family physicians, psychologists, behavioral scientists, social workers, graduate students, and all members of the health care team who share an interest in understanding and treating the older individual with Alzheimer's disease and his family.

Nancy E. Miller
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Acknowledgments

This volume is derived from the proceedings of the Second International Conference on Alzheimer's Disease and Senile Dementia, jointly hosted by the National Institute of Mental Health, the National Institute on Aging, and the National Institute of Neurological and Communicative Disorders and Stroke and held on the campus of the National Institutes of Health in Bethesda, Maryland. The proceedings of the First Conference[1] focused on basic research in the etiology, pathophysiology, nosology, and epidemiology of this brain disorder. The emphasis of this Second Conference is on current clinical research and practice in the assessment, differential diagnosis, care, and treatment of the Alzheimer's patient within a practical and multidisciplinary framework.

[1] Katzman, R., Terry, R. D., and Bick, K. L., editors (1978): *Alzheimer's Disease: Senile Dementia and Related Disorders* (Aging, Vol. 7). Raven Press, New York.

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Introductory Statement: A View from the Alcohol, Drug Abuse, and Mental Health Administration

Gerald L. Klerman

Alcohol, Drug Abuse, and Mental Health Administration, Rockville, Maryland 20857

The clinical aspects of Alzheimer's disease and senile dementia—the disorders of later life—is an area of great concern across a range of categorical programs. The Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) is pleased to join the National Institute on Aging and the National Institute of Neurological and Communicative Disorders and Stroke in discussing this important area.

NIH and ADAMHA together fund approximately 90% of the nation's research in the biomedical, behavioral, and psychosocial aspects of health and illness.

Each of the three component Institutes of ADAMHA—the National Institute of Mental Health, the National Institute on Alcoholism and Alcohol Abuse, and the National Institute of Drug Abuse—has a particular and vital interest in the problems of aging.

The National Institute of Mental Health, with its Center for studies of the Mental Health of the Aging, has had the lead in the development of this conference. Such collaboration represents a dynamic aspect of the American research establishment, both in intramural and extramural programs. We have discovered various means of working together on large scale problems that cut across the categorical Institutes, while at the same time developing research focused on a particular manifestation of the problem.

This is the second joint conference called to deal with the problems of the dementias. That a distinguished group of investigators has again been brought together for these discussions indicates once again the capacity of the Public Health Service and of the scientific community to mobilize research efforts and knowledge for the further understanding of large-scale health problems.

It is our experience that through the valuable combination of basic and clinical research, public health problems can and do lend themselves to amelioration. Our continuing commitment to a balance between basic and clinical research stands as a fundamental principle of all our scientific endeavors, and particularly in the field of aging.

In the past the National Institute of Mental Health and the other Institutes

of our agency may have emphasized the psychosocial and behavioral aspects of Alzheimer's disease, senile dementia, and other disorders. However, in recent years, the Institutes have supported increased activity in the neurosciences, including genetics, neurochemistry, and neuropharmacology. The boundaries between the biomedical and the behavioral sciences are increasingly becoming blurred; the distinctions between the purely behavioral and the biomedical approaches to a problem such as aging are more difficult to maintain. In this and other areas, as much cooperation is now required among the various scientific disciplines as has been required in the cooperation of several distinct Institutes in developing this series of conferences.

There have been notable advances in the basic neurosciences, especially in the understanding of the structure and functioning of the central nervous system, and in the psychological sciences, particularly as to the regulation of mood as occurs in depression among the aged, and the processes of memory and of cognition in aging. The clinical distinction between the pseudo-dementias of the depressions and the true dementias remains a major research problem to be addressed by the field.

I look forward to participating in these scientific deliberations and urge the three Institutes to plan other collaborative endeavors in this and other areas.

ENCLOSURE # 4

CURRENT NIMH RESEARCH ON ALZHEIMER'S DISEASE

Joseph Barbaccia, M.D.
University of California, San Francisco
"Adjustment of Older Persons After Acute Hospitalization"
$70,000 #32731

This study addresses the long-term impact of physical illness on cognition, as well as the impact of social support upon the physical and mental health of older individuals over time.

Joseph Becker, M.D.
University of Washington, Seattle, Washington
"Stress Vulnerability in Alzheimer's Patients' Families"
$231,542 #33779

Family members caring for Alzheimer's patients are subjected to severe stresses and may be at especially high risk for depressive reactions. This study investigates stressors, moderating variables and adaptation in families of Alzheimer patients and controls. The inability to alter the course of the disease, the demanding care reauired, and the inevitable bereavement make depressive reactions especially probable. Two related theories of vulnerability to depressive reactions will be tested in this investigation, Brown's social-network-self-esteem theory, and Seligman's attributional theory of learned helplessness.

Elaine M. Brody, M.S.W.
Philadelphia Geriatric Center
"Women, Work, and Care of The Aged: Mental Health Effect"
$318,000 #35352

This study investigates the impact of paid employment of the daughter on the perceived burdens related to care of a parent with dementing and other mental disorders. The project addresses the impact of two converging social trends on each other--the fact that the proportion of the "very old", those most in need of supportive services, is increasing more rapidly than the total elderly population, at the same time that women in their middle years, the traditional caregivers to noninstitutionalized elderly, are increasingly employed outside the home. While the maintenance of older demented individuals in noninstitutional living arrangements depends largely on the familys' capacity to provide services, there is as yet no systematic information regarding the actual effect of the work status of caregivers on the mental health of the elderly, on the caregiving generation of women themselves and other family members, and on the formal social/health support system, as shifts occur in the allocation of parent-care task. This proposal will provide new information on these parameters.

Jonathan O. Cole, M.D.
Boston Mental Health Foundation, Inc.
Boston, Mass.

"Lecithin in Senile Dementia"
$125,000 #33699

This project will undertake two parallel studies of cholinominetic agents in the treatment of senile and presenile dementia of the Alzheimer's type. One study is a 12-week, double blind trial of oral lecithin in outpatients with mild dementia, and the other is a trial of acute physostigmine and arecoline and chronic lecithin in hospitalized patients with more severe dementia. Both studies will investigate the possible effects of increasing cholinergic activity on mental deficits associated with senile dementia.

Carl I. Cohen, M.D.
New York University, N.Y.
"Old Men on the Bowery in the 1980's: Adaptive Strategies".
$155,050 #35724

Utilizing a variety of validated biographic, demographic, diagnostic and psychosocial inventories, the investigator is conducting an epidemiologic analysis in order to ascertain the prevalence of senile dementia in a high risk group of older men living on New York City's Bowery. The study will examine the clinical course of illness, and explore the coping mechanisms utilized by these men in surviving.

Suzzane H. Corkin, Ph.D.
Massachusetts Institute of Technology
Cambridge, Massachusetts
"Lecithin Precursor Treatment in Alzheimer's Disease"
$255,654 #32724

This project will investigate the possibility of using cholinergic agents for the purpose of reversing the deficits in cognitive and behavioral functioning associated with Alzheimer's disease. The study includes double-blind studies on the effects of lecithin in combination with physostigmine or piracetam,tyrosine, or tryptophan on memory, cognitive functioning, and a variety of biological measures (e.g., spinal fluid levels of several peptides, neurotransmitter metabolites and proteins, and urine levels of melatonin).

Joseph T. Coyle, M.D.
Johns Hopkins University
Baltimore, Maryland
"Neuropsychiatric Disorders: Selective Neural Loss"
$183,750 #00125

This Research Scientist Development Award, Level II, is for support of Dr. Coyle's studies of the cholinergic deficits in Senile Dementia of the Alzheimer's type. His major goal is to define the neuronanatomical organization and synaptic chemistry of the cholinergic innervation to the cerebral cortex and the alterations produced by selective ablation of the basal forebrain

cholinergic pathways in the rat, in an effort to relate these to the pathophysiology of Alzheimer's dementia. On the basis of experimental electrothermic and excitotoxin lesioning of the rat basal forebrain in the ventral globus pallidus, and on the basis of collaborative autopsy studies of Alzheimer's dementia, showing profound degeneration of the nucleus Basilis of Meynert and related basal forebrain cholinergic projections, Dr. Coyle has suggested that degeneration of cholinergic pathways constitutes at lease a significant part of the pathophysiology of Alzheimer's disease.

Steven H. Ferris
New York University, New York, N.Y.
"Neurometric Assessment of Mental Health in Aging"
$371,419 #32577

This is a study which extends previous research concerned with the neurometric evaluation of normal and cognitively impaired elderly individuals. Using EEG and evoked potential recording methodology, the investigator is developing differential diagnostic procedures for senile dementia based on the hypothesis that the two hemispheres of the brain may derive conflicting interpretation of incoming information.

Ajax E. George, M.D.
New York University, New York, N.Y.
"Mental Health, Brain Impairment and Aging".
$380,951 #36969

This project aims to study Senile Dementia of the Alzheimer's Type (SDAT) over time with computerized tomography and psychological testing in order to elucidate the progression and brain regional representation of SDAT. The investigators will develop and refine techniques which will measure the parenchymal changes (grey and white matter density measures as well as the grey-white matter discriminability) noted on the CT of Alzheimer's patients and correlate these changes with those documented via a neuropsychological test battery.

Lissy F. Jarvik, M.D.
University of California, Los Angeles, Calif.
"Alzheimer Type Dementia: A Biobehavioral Family Study"
$800,892 #36205

The purpose of this study is to investigate the biopsychological characteristics of individuals who develop dementia in old age. The investigator will determine whether patients with SDAT have a higher frequency of cytogenic (aneuploid) and/or immune (immunoglobulin levels) changes than patients with multi-infarct dementia (MID) or major depressive disorder, or age-matched controls; and whether SDAT patients have psychometric profiles which differ significantly from patients with depression, but not from those with MID. The study will also evaluate whether first-degree relatives of SDAT patients show similar biological and/or premorbid psychometric changes, and whether these individuals are actually at increased risk for developing SDAT.

Ira R. Katz, M.D.
Yeshiva University
Bronx, New York
"Mental Health and Aging: Delineation of Depression"
$321,676 #37026

This study will evaluate the identification and diagnosis of affective disorder in elderly persons with dementing illness. The investigation will also investigate the impact of anti-depressant treatment on memory, cognition, and the ability to successfully carry the activities of daily living. The treatment study is a double-blind randomized trial of Nortriptyline or Placebo. Subjects will be studied with respect to symptoms, previous psychiatric history, family history of psychiatric disorder, recent stressful life events, functional disability, concurrent medical diagnosis, and the dexamethasone suppression test.

Marlyne Kilbey, Ph.D.
Middle Tennessee State University - Murfreesboro, Tenn.
"Age Effects in Animal Models of Abnormal Behavior"
$30,278 #34277

This project is studying age-related differences in the effects of drugs on the behavior of rats under conditions thought to mimic human disease states, including progressive dementia. The study will characterize some of the neuroanatomical mechanisms which underlie the brain changes with disease, by evaluating the development of kindling seizures, which have, in prior research, been linked to the depletion of brain catecholamines.

Eric B. Larson, M.D., MPH
University of Washington
Seattle, Washington
"Dementia and Mental Health in the Aged"
$111,610 #33841

The aim of this project is to discover the diagnostic yield and cost effectiveness of a thorough evaluation designed to detect reversible causes of dementia in the elderly. The study will assess the outcome of dementia and the degree to which treatment of "reversible" dementia actually improves cognitive function and patient outcome. It is believed that 10-30 percent of all patients with dementia have an underlying unrecognized treatable cause. However, the cost of minimally effective screening evaluation is $500-1,000, depending on the abnormalities detected. Thus, the overall cost of evaluating 1,000,000 patients annually could approach one billion dollars. On the other hand, some authorities feel that the cost of a full workup to uncover unreversible causes for intellectual impairment in the elderly is more than compensated for by reduction in costs of treatment in nursing homes or other long term care facilities. This project comprises a beginning step towards the evaluation of these issues.

M. Powell Lawton, Ph.D.
Philadelphia Geriatric Center
Philadelphia, Pa.
"The Last Year of Life: Mental Health Aspect"
$289,968 #37707

This project aims to increase our systematic knowledge of the last year of life as it is lived by the elderly individual, at home in the community, as a function of cognitive status, physical health, independence in performing self-care and the instrumental tasks of daily living, the use of time, and attitude towards death.

Robert J. Nathan, M.D.
Hahnemann Medical College
"Aging: Brain Structures and Sociobehavioral Variables"
$186,411 #37281

The investigator hypothesizes that the psychobehavioral manifestation of senile behavioral changes are more directly related to socio-cultural factors than to structural changes in the brain or to previous personality characteristics. By longitudinally following two concurrent samples of an aged white population, in order to determine what changes take place using neuropsychological test batteries, functional assessments, computerize axial tomography, psychiatric evaluations, physical examinations, and blood chemistries, the investigator aims to determine how socio-demographic characteristics and behavioral parameters interact with levels of organicity in affecting the capacity of the individual to live independently in the community.

George Niederehe
Texas Research Institute of Mental Sciences
Houston Texas
"Family Dynamics and the Care of Aged with Dementia,"
$199,853 #35400 (1)

This project aims to longetudinally study the adjustment of the families of elderly demented individuals over an extended period. The study will evaluate in detail, the interpersonal relationships within these families; the well-being of family members as a function of the dementia of the impaired relative, types of families and phases of family organization, including the identification of factors which facilitate optimum family coping, and the influence of the interpersonal context on the course of dementing process and on manifest symptomatology.

Erdman B. Palmore, Ph.D.
Duke University
Durham, North Carolina
"Mental Illness and Social Support Among the Very Old"
$345,000 #33704

This study will examine the antecedents and consequences of organic and affective mental illness in individuals over the age of 75, who have been participants in a comprehensive longitudinal investigation begun in 1972. The study includes complete physical examinations, medical histories, blood chemistries, EKGs, EEGs, cerebral

Palmore (Continued)

blood flow studies, structured psychiatric examinations, neuropsychological batteries, life stress interviews, social evaluations, etc.

Walter S. Poulshock, Ph.D.
Benjamin Rose Institute
"Caring for Elders and Mental Health of Family Members"
$300,000 #35360

This study of cognitively impaired elderly and the family members who provide care for them views the caregiving situation as a process in which stress and its effects have consequences for the mental health of all family members. This study will examine the processes involved in families solving or failing to solve the problems posed by supporting impaired elderly parents living in their own homes, and will measure the amount of stress consequent upon specific problems in family mobilization and provision of support.

Patricia Prinz, Ph.D.
University of Washington
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"Sleep/Waking Patterns in Dementia"
$231,739 #33688

The objective of this study is to compare dementia with normal aging in an effort to describe the nature of selected neurobiological factors underlying the onset and progression of the dementing process. The study is designed to evaluate sleep pattern and mental function variables in patients diagnosed with Senile Dementia of the Alzheimer's type. Electrophysiological variables will be measured, including degree of alpha frequency decline, diffuse waking EEG slowing; sleep slow wave activity; rapid eye movement variables, sleep fragmentation, spindle frequency, and other rhythmic EEG changes.

Burton T. Reifler, M.D.
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"Mental Health in the Aged: Combined Dementia and Depression"
$233,698 #36596

This is a study to determine whether elderly patients with a dementing illness (Alzheimer's disease or multi-infarct dementia) but who are not depressed, differ with respect to antecedents and outcome from patients who are demented and also depressed. The project will determine whether demented patients who are depressed can improve in memory and cognitive ability following treatment with a tricyclic antidepressant (imipramine). Data will be collected on previous psychiatric history, type of dementia, living situation, significant demographic variables, and on long term outcome.

Walter Riege, Ph.D.
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"Non-Verbal Memory in the Aged Mentally Healthy or Ill"
$91,058 #32172

The investigator hypothesizes that not all memory functions are affected equally by age and by dementia. The investigators seek to determine whether normal and demented elderly are different in the speed and cautiousness they manifest in encoding and retrieving non-verbal information from short-term memory.

Joanne Steuer, Ph.D.
University of California
Los Angeles, California
"Support Groups for Families of Dementia Patients"
$44,650 #37053

This research is designed to evaluate the efficacy of support groups for caregivers of elderly patients diagnosed as having primary degeneration or multi-infarct dementia. Group treatment will be compared with a waiting list control group. Outcome will be assessed by change in depression, anxiety, life satisfaction, feelings of burden, and changes in number and intensity of pleasurable events in which subjects participate. Additional information for assessing outcome will be provided by a questionnaire containing items pertaining to help seeking behaviors of the caregivers, and time spent away from the patient.

Jared Tinklenberg, M.D.
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"Neuropeptides, Mood, and Memory in the Elderly"
$163,553 #36609

This is a proposal to investigate the effects of two vasopressin analogs and an ACTH fragment on certain cognitive tasks in elderly individuals with mild-to-severe intellectual and memory impairment. The agents to be studied are: 1) desamino-8-D-arginine vasopressin (DDAVP), and 3) ACTH 4-9. The use of these substances is based on findings by DeWied and others that administration of vasopressin as well as certain ACTH fragments to animals interefered with extinction of a conditioned response. The present proposal aims to evaluate the relationship of this phenomenon to human learning and memory.

George E. Vaillant, M.D.
Harvard University
Cambridge, Mass.
"Effect of Mental Health on Aging"
$361,021 #32885

The purpose of this study is to identify the premorbid psychological predictors of early aging, and to follow the significant deterioration of physical and cognitive function in men longitudinally studied since adolescence for forty years, who are now in late middle age, and entering old age.

Bart P. Vrtunski, Ph.D.
Case Western Reserve University
Cleveland, Ohio
"Psychomotor Slowing and Age: Microbehavioral Analysis"
$81,185 #33181

By utilizing a microbehavioral analysis of motor activity to a choice and reaction time task for the purpose of providing greater understanding of decision-making, response selection, and response execution processes, the investigator intends to enhance the difficult process of differential diagnosis between elderly clinical groups known to exhibit psychomotor impairment--e.g. senile dementia of the Alzheimer's type and major affective disorder.

Steven H. Zarit, Ph.D.
University of Southern California
Los Angeles, California
"Family Interventions for Senile Dementia"
$267,000 #34507

This study evaluates an innovative program of individual and family counseling for caregivers of older people with senile dementia, as a way of reducing the burden of care and making home placement feasible for families who desire it.

George Niederehe, Ph.D.
Texas Research Institute of Mental Sciences
"Memory Impairment in Affective Disorders of the Aged"
$89,113 #30664

This study will investigate whether aging depressed persons show altered control processes in memory, or different knowledge about their memory system. It will evaluate cognition in that borderline area of diagnosis between the affective and organic psychiatric disorders in man.

NIMH RESEARCH ON ALZHEIMER'S DISEASE

Grant #	PI	Title	Total Cost
32731	Barbaccia	Adjustment of Older Persons After Acute Hospitalization	$ 70,000
33779	Becker	Stress Vulnerability in Alzheimer's Patients Families	231,542
35352	Brody	Women, Work, and Care of the Aged: Mental Health Effect	318,000
33699	Cole	Lecithin in Senile Dementia	125,000
35724	Cohen	Old Men on the Bowery in the 1980's: Adaptive Strategies	155,050
32724	Corkin	Lecithin Precursor Treatment in Alzheimer's Disease	255,654
00125	Coyle	Neuropsychiatric Disorders: Selective Neural Loss	183,750
32577	Ferris	Neurometric Assessment of Mental Health in Aging	371,419
36969	George	Mental Health, Brain Impairment and Aging	380,951
36205	Jarvik	Alzheimer Type Dementia: A Biobehavioral Family Study	800,892
37026	Katz	Mental Health and Aging: Delineation of Depression	321,676
34277	Kilbey	Age Effects in Animal Models of Abnormal Behavior	30,278
33841	Larson	Dementia and Mental Health in the Aged	111,610
37707	Lawton	The Last Year of Life: Mental Health Aspect	289,968
37281	Nathan	Aging: Brain Structures and Sociobehavioral Variables	186,411
35400	Niederehe	Family Dynamics and the Care of Aged with Dementia	199,853
33704	Palmore	Mental Illness and Social Support Among the Very Old	345,000
35360	Poulshock	Caring for Elders and Mental Health of Family Members	300,000
33688	Prinz	Sleep/Waking Patterns in Dementia	231,739
36596	Reifler	Mental Health in the Aged: Combined Dementia and Depression	233,698
32172	Reige	Non-Verbal Memory in the Aged Mentally Healthy or Ill	91,058

NIMH RESEARCH ON ALZHEIMER'S DISEASE

Grant #	PI	Title	Total Cost
37053	Steuer	Support Groups for Families of Dementia Patients	$ 44,650
36609	Tinklenberg	Neuropeptides, Mood, and Memory in the Elderly	163,553
32885	Vaillant	Effect of Mental Health on Aging	361,021
33181	Vrtrunski	Psychomotor Slowing and Aging: Microbehavioral Analysis	81,185
34507	Zarit	Family Interventions for Senile Dementia	267,000
30664	Niederehe	Memory Impairment in Affective Disorders of the Aged	89,113

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
National Institutes of Health

Memorandum

Date June 15, 1983

From Acting Deputy Director, NINCDS

Subject Grassley Hearing on Alzheimer's Disease; Our telephone conversation of June 14

To Ms. Kay Holcombe, DLA-OD

The two international conferences on Alzheimer's Disease sponsored by NINCDS, NIMH and NIA in 1977 and 1978 have, in retrospect, proved to be the important stimulus for the remarkable resurgence in reseach in Alzheimer's Disease. This year, for example, there will be at least three (3) international meetings with non-federal sponsors devoted to research findings in various aspects of Alzheimer's disease. In 1984 and 1985, several others are planned including that by the World Federation of Neurology which will have Alzheimer's Disease and the Dementias as a major theme (Public Health Service investigators will participate with their international colleagues). As a consequence of this activity, the PHS has no immediate plans to program further international meetings.

The NINCDS, as part of its activities as a WHO Collaborating Center for Research in the Neurological Disorders, has begun studies to determine prevalence of Alzheimer's Disease and to identify possible risk factors for dementia. This study has been initiated in Nigeria, China, Mexico, and Peru. Programs are planned in Ecuador and Spain. Analysis of these data should enable us to develop better understanding of the disease.

The NINCDS has initiated a bilateral agreement with Italy to study Alzheimer's Disease and the dementias in both countries using similar methodologies. Initial investigations will focus on studies of families with several cases of the disease.

Katherine L. Bick

Katherine L. Bick, Ph. D.

Senator GRASSLEY. I want to thank all of you for being so patient for the hour and a half you have been waiting to testify.

Thank you very much.

Dr. GOLDSTEIN. Thank you.

Dr. RINGLER. Thank you, Mr. Chairman.

Dr. PARDES. Thank you for your interest, Senator.

Senator GRASSLEY. Our next panel of witnesses includes Dr. Barry Reisberg, clinical director of the geriatric treatment and study program, New York University; Ms. Nancy Mace, assistant in psychiatry and coordinator of the T. Row and Eleanor Price Teaching Service at Johns Hopkins University, and Dr. Tony Damasio, professor of neurology at the University of Iowa College of Medicine, Iowa City, Iowa.

And, not to detract from the other two participants, but I want to remind you that Dr. Damasio is a constituent of mine. We appreciate his leadership in this area at the University of Iowa, and particularly appreciate his coming out here despite an otherwise busy schedule, I know, to participate in this hearing.

Would you proceed first, Dr. Reisberg?

STATEMENT OF DR. BARRY REISBERG, CLINICAL DIRECTOR, GERIATRIC TREATMENT AND STUDY PROGRAM, NEW YORK UNIVERSITY; NANCY L. MACE, ASSISTANT IN PSYCHIATRY, AND COORDINATOR, T. ROWE & ELEANOR PRICE TEACHING SERVICE, DEPARTMENT OF PSYCHIATRY AND BEHAVIORAL SCIENCES, JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE; AND DR. TONY DAMASIO, PROFESSOR OF NEUROLOGY, UNIVERSITY OF IOWA, A PANEL

Dr. REISBERG. Mr. Chairman, as stated, until recently, Alzheimer's disease was largely neglected by both laymen and physicians alike, and usually not distinguished from aging in general. However, in recent years, both physicians and laymen have shown increased interest in this disorder.

In the past decade, an enormous amount of progress has been made in the understanding of Alzheimer's disease by scientists around the world. Some examples of what has been done about this terrible disease in the past decade include the following. The clinical characteristics of the illness process, how it evolves, and the impact of this process on patients and their families, has been described in detail for the first time. Detailed case histories have been published describing the stages of the disease. The clinical characteristics of each stage of the illness have been determined, enabling doctors to more accurately diagnose the illness at each phase of its evolution. Guidelines for treatment and management at each stage have been developed. These include guidelines not only for caring for the patients themselves, but also for alleviating the burden of family members who must share their suffering.

Considerable knowledge has been gained with respect to the structural, chemical and functional brain changes accompanying the illness process. Newly developed brain-imaging techniques have enabled us to demonstrate that, as the illness evolves, the fluid filled cavities deep within the brain expand, and the grooves or sulci on the surface of the brain become wider and deeper. Other

investigations have demonstrated that microscopic structural brain changes occur in this illness, not only on the brain surface, but also in regions deep within the brain.

Various brain chemical alterations have been found to accompany the Alzheimer's disease process. Chemical messenger systems in the brain have been found to be progressively depleted or altered. Certain chemical messenger systems in the brain have been shown to be selectively affected. Technological advances which have occurred in the past decade have also enabled us to demonstrate that progressive decreases in the energy utilization of the brain also accompany the progression of Alzheimer's disease. These changes in brain energy utilization or metabolism do not appear to be a part of the normal aging process, but only appear to occur as the disease progresses.

These basic findings, with respect to the nature of Alzheimer's disease, have been coupled with efforts to improve the treatment of this dreaded disorder.

Guidelines for the utility of traditionally available treatments in alleviating the secondary symptoms of the disorder have been formulated. Simultaneously, numerous new drug treatments specific for this disease have been carefully evaluated. These include drugs which improve brain blood flow and energy utilization, drugs which increase the levels of brain chemicals and chemical messengers, drugs which specifically appear to affect cognition and intelligence, and new classes of drugs which have only recently been shown to play a useful role in the chemistry of the brain.

Many traditional treatments have been shown to be of questionable value. Other treatment approaches are presently showing promise.

Efforts are also under way which combine our increased understanding of the manifestations and diagnosis of the disorder, with advances in our technologic capabilities, and with our enhanced knowledge of the chemical alterations in the brain substance.

For example, within the next few months, scientists will administer possibly useful treatments to patients with this disease, and using the new positron emission tomographic scanning techniques, directly observe the effects of these drugs on pictures reflecting the brain's energy utilization. Such procedures should enable doctors to directly determine the effects of a particular drug on a particular patient at a particular dosage, and at a particular time. This information may enable doctors and scientists to markedly shortcut the laborious procedures involved in drug testing and evaluation.

In summary, Alzheimer's disease is truly a major medical disorder. It is also an illness which had, until recently, been singularly neglected by laymen and physicians alike. There are very few individuals in our Nation who are fortunate enough to go through life without being personally touched by heart disease and cancer. Similarly, there are very few persons in our society who do not have a spouse, a parent, a grandparent, or a close relative with Alzheimer's disease in its moderate to severe forms. The sickness, suffering, and death caused by Alzheimer's disease are also comparable to that of heart disease and cancer. However, the research efforts, in both dollars and personnel, devoted to this illness in the

past decade has been only a very small fraction of that for heart disease or cancer.

Nevertheless, this research has resulted in contributions over the past decade which rival those made in our understanding of almost any other medical condition.

As a major illness which touches virtually everyone, Alzheimer's disease is also a major illness in which virtually everyone has a stake. The cost of caring for an Alzheimer's sufferer in the home are such as to eventually exhaust the resources of even our most affluent citizens. The human costs in suffering and despair are of course incalculable.

Hence, this disease is costly not only to the government and its citizens but also to all of the major institutions in this country. Therefore, it is notable that some of the earliest efforts to identify effective treatments for this disease were collaborative efforts between governmental, academic, and industrial organizations. I believe it is fair to say that a small investment has already resulted in enormous dividends for all of these constituencies. I also predict that future dividends from investigations into this, until recently, spectacularly neglected illness will be at least equally great.

Thank you, Senator.

[The prepared statement of Dr. Reisberg follows:]

MAY 12 1983

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School of Medicine

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Department of Psychiatry

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May 10, 1983

Millhauser Laboratories (HN 314)

Committee on Labor
and Human Resources
United States Senate
Washington, D.C.

Dear Sirs:

Alzheimer's disease, the major form of what is commonly termed "senile dementia," is a major illness. Estimates indicate that, in the population aged 65 years and older, the prevalence of severe dementia is 4%-5% and the prevalence of mild to moderate dementia is 11%-12%. On the basis of these percentages one might expect that in the United States approximately 1 million elderly people are afflicted with severe dementia and another 3 million with mild to moderate dementia (1). Tragically, many thousands of Americans also succumb to this condition earlier in life. Individuals in their early to mid-fifties with moderate to severe Alzheimer's disease are not at all uncommon.

U.S. government statistics show that chronic organic brain syndromes, presumably secondary in most cases to senile dementia of the Alzheimer's type, afflict 58% of the more than 1 million Americans in nursing homes (report from the National Center on Health Statistics, 1978). In the survey, all forms of arthritis combined, and all forms of heart disease combined each afflicted only approximately a third of the U.S. nursing home population. Hence, Alzheimer's disease is by a broad margin the most prevalent condition in American nursing homes. Since there are more Americans in nursing homes than in all forms of hospitals combined (including veterans hospitals, state hospitals, county hospitals, private and voluntary facilities, etc.), these statistics are particularly disturbing.

Many senile dementia patients are housed in other chronic-care institutions such as state mental hospitals and Veterans Administration hospitals. More than half of the patients over age 65 in state and county mental hospitals also carry the diagnosis of chronic organic brain syndrome or senile dementia.

Studies of patients with senile dementia have shown a marked decrease in life expectancy. A calculation from the prevalence data indicates that senile dementia, secondary in most cases to Alzheimer's disease, may account for 100,000-120,000 deaths annually in the United States. Senile dementia is thus the fourth leading cause of death in this country and other developed nations. As a cause of suffering and death, it is comparable in magnitude to such major

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illnesses as cancer and heart disease (1).

Until recently, this major disease was largely neglected by both laymen and physicians alike, and usually not distinguished from aging in general. However, in recent years, both physicians and laymen have shown increased interest in this disorder. In the past decade an enormous amount of progress has been made in the understanding of Alzheimer's disease by scientists around the world (2-4).

Some examples of what has been done about this terrible disease in the past decade including the following:

(1) The clinical characteristics of the illness process, how it evolves, and the impact of this process on patients and their families, has been described in detail for the first time.

Detailed case histories have been published describing the stages of the disease (2). The clinical characteristics of each stage of the illness have been determined, enabling doctors to more accurately diagnose the illness at each phase of its evolution (5, 6). Guidelines for treatment and management at each stage have been developed (7). These include guidelines not only for caring for the patients themselves, but also for alleviating the burden of family members who must share their suffering.

(2) Considerable knowledge has been gained with respect to the structural, chemical, and functional brain changes accompanying the illness process.

Newly developed brain imaging techniques have enabled us to demonstrate that, as the illness evolves, the fluid-filled cavities deep within the brain expand and the grooves, or sulci, on the surface of the brain become wider and deeper (8). Other investigations have demonstrated that microscopic structural brain changes occur in this illness not only on the brain surface, but also in regions deep within the brain (9).

Various brain chemical alterations have been found to accompany the Alzheimer's disease process. Chemical messenger systems in the brain have been found to be progressively depleted or altered. Certain chemical messenger systems in the brain have been shown to be relatively selectively affected (10).

Technologic advances which have occurred in the past decade, have also enabled us to demonstrate that progressive decreases in the energy utilization of the brain also accompany the progression of Alzheimer's dementia (11). These changes in brain energy utilization or "metabolism," do not appear to be a part of the normal aging process, but only appear to occur as the disease progresses.

(3) These basic findings, with respect to the nature of Alzheimer's disease, have been coupled with efforts to improve the treatment of this dreaded disorder.

Guidelines for the utility of traditionally available treatments in alleviating the secondary symptoms of the disorder have been formulated. Simultaneously, numerous new drug treatments, specific for this disease, have been carefully evaluated (12). These include drugs which improve brain blood flow and energy utilization, drugs which increase the levels of brain chemicals and chemical messengers, drugs which specifically appear to affect cognition and intelligence, and, new classes of drugs which have only recently been shown to play a useful role in the chemistry of the brain.

Many traditional treatments have been shown to be of questionable value. Other treatment approaches are presently showing promise.

(4) Efforts are also underway which combine our increased understanding of the manifestations and diagnosis of the disorder, with advances in our technologic capabilities, and with our enhanced knowledge of the chemical alterations in the brain substance.

For example, within the next few months, scientists will administer possibly useful treatments to patients with this disease and, using the new positron emission tomographic scanning techniques, directly observe the effects of these drugs on pictures reflecting the brain's energy utilization. Such procedures should enable doctors to directly determine the effects of a particular drug, on a particular patient, at a particular dosage, and at a particular time. This information may enable doctors and scientists to markedly shortcut the laborious procedures involved in drug testing and evaluation.

In summary, Alzheimer's disease is truly a major medical disorder. It is also an illness which had, until very recently, been singularly neglected by laymen and physicians alike. There are very few individuals in our nation who are fortunate enough to go through life without being personally touched by heart disease and cancer. Similarly, there are very few

Committee on Labor
& Human Resources

May 10, 1983

persons in our society who do not have a spouse, a parent, a grandparent, or a close relative whith Alzheimer's disease in its moderate to severe forms. The sickness, suffering, and death caused by Alzheimer's disease are also comparable to that of heart disease and cancer. However, the research effort, in both dollars and personnel, devoted to this illness in the past decade has been perhaps only one percent of that for heart disease or cancer. Nevertheless, this research has resulted in contributions over the past decade which rival those made in our understanding of almost any other medical condition.

As a major illness which touches virtually everyone, Alzheimer's disease is also a major illness in which virtually everyone has a stake. The cost of nursing home care in the U.S. in 1982 was approximately 20 billion dollars. Alzheimer's disease accounts for a major portion of that cost. The costs of caring for an Alzheimer's sufferer in the home are such as to eventually exhaust the resources of even our most affluent citizens. The human costs in suffering and despair are of course incalculable.

Hence, this disease is costly not only to the government and its citizens, but also to all of the major institutions in this country. Therefore, it is notable, that some of the earliest efforts to identify effective treatments for this disease were collaborative efforts between governmental, academic, and industrial organizations (13). I believe it is fair to say that a small investment has already resulted in enormous dividends for all of these constituencies. I also predict that future dividends from investigations into this, until recently, spectacularly neglected illness, will be at least equally great.

Sincerely,

Barry Reisberg

BR:gg

Barry Reisberg, M.D.
Clinical Director
Geriatric Study & Treatment Program
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New York University Medical Center

REFERENCES

1. Schneck, M.K., Reisberg, B., and Ferris, S.H., "An Overview of Current Concepts of Alzheimer's Disease," American Journal of Psychiatry, 139: 165-173, 1982 (enclosed).

2. Reisberg, B. Brain Failure: An Introduction to Current Concepts of Senility, The Free Press (Macmillan Pub. Co.), New York, 1981, 198 pages (enclosed).

3. Katzman, R., Terry, R.D., and Bick, K.L. (Eds.), Alzheimer's Disease and Related Disorders, Aging, Vol. 7, Raven Press, New York, 1978, 595 pages.

4. Miller, N.E. and Cohen, G.D. (Eds.), Clinical Aspects of Alzheimer's Disease and Senile Dementia, Aging Vol. 15, Raven Press, New York, 1981, 357 pages.

5. Reisberg, B., Ferris, S.H., de Leon, M.J., and Crook, T., "The Global Deterioration Scale (GDS): An Instrument for the Assessment of Primary Degenerative Dementia (PDD)," American Journal of Psychiatry, 139:1136-1139, 1982 (enclosed).

6. Reisberg, B., and Ferris, S.H., "Diagnosis and Assessment of the Older Patient," Hospital and Community Psychiatry, 33:104-110, 1982 (enclosed).

7. Reisberg, B., "The Office Management of Primary Degenerative Dementia," Psychiatric Annals, 12:6, 631-637, 1982 (enclosed).

8. de Leon, M.J., Ferris, S.H., George, A.E., Reisberg, B., Kricheff, I.I., and Gershon, S., "Computed Tomography Evaluations of Brain-Behavior Relationships in Senile Dementia of the Alzheimer's Type," Neurobiology of Aging, 1:69-79, 1980 (enclosed).

9. Coyle, J.T., Price, D.L., and De Long, M.R., "Alzheimer's Disease: A Disorder of Cholinergic Innervation," Science, 219:1184-1190, 1983 (enclosed).

10. Bartus, R.T., Dean, R.L., Beer, B., and Lippa, A.S., "The Cholinergic Hypothesis of Geriatric Memory Dysfunction," Science, 217:408-417, 1982 (enclosed).

11. Ferris, S.H., de Leon, M.J., Wolf, A.P., Farkas, T., Christman, D.R., Reisberg, B., Fowler, J.S., MacGregor, R., Goldman, A., George, A.E., and Rampal, S., "Positron Emission Tomography in the Study of Aging and Senile Dementia," Neurobiology of Aging, 1:127-131, 1980 (enclosed).

12. Reisberg, B., Ferris, S.H., and Gershon, S., "An Overview of Pharmacologic Treatment of Cognitive Decline in the Aged," American Journal of Psychiatry, 138:593-600, 1981 (enclosed).

13. Crook, T., and Gershon, S. (Eds.), Strategies for the Development of an Effective Treatment for Senile Dementia, Mark Powley Associates, New Canaan, Conn., 1981, 320 pages (enclosed).

Senator GRASSLEY. Thank you, before I ask questions, if you could wait, I would like to have the others testify. I will mention the book that you authored, "Brain Failure: An Introduction to Current Concepts of Senility." I apologize for not mentioning your contribution to knowledge in this area at the outset as a demonstration of your outstanding reputation that you have.

I know also that you coauthored a book called, "The 36-Hour Day: A Family Guide to Caring for Persons with Alzheimer's Disease, Related Dementing Illnesses, and Memory Loss in Later Life." That is a leading resource in this area, as well, contributing to today's knowledge in this area, by informing people how they can cope with a loved one's condition. Is that one of the ways we could characterize what you have to say?

Ms. MACE. Absolutely, Senator.

Senator GRASSLEY. OK. Please, proceed.

Ms. MACE. I want to thank you for the opportunity to testify on behalf of the families and what they need, as you say, while they wait.

I am only going to summarize my written testimony.

Senator GRASSLEY. And we will include your written testimony in the record.

Ms. MACE. Fine. I gave a lot of thought to whether or not to bring you primarily numbers or primarily human costs, and I think both are important. The other people testifying have told you that there will be much better numbers as to how many people this afflicts and the effect it has upon families is.

One of the important studies, of course, will be the epidemiologic study, which will soon be giving us a better understanding of how many people are afflicted.

But I think it is important to consider that most elderly people have spouses, have children, have grandchildren, and many of them have great-grandchildren, so the implications of the disease extend far beyond the victim himself.

I am going to describe briefly what a person with Alzheimer's disease is like, and as I do, think about what it would be like to go home to this at the end of the day.

It is a disease of insidious onset and devastating course. Its initial symptom is loss of recent memory. Early in the course of the disease, the patient may realize what is happening to him and be depressed, or he may be more anxious and irritable than previously. Often, couples seek couples therapy for the first time in their marriage because something is wrong, and they do not recognize what is indeed happening. Patients lose their jobs. They have automobile accidents for the first time. They are suspected of being drinkers when in fact, they are not. As the patient's illness progresses, he will need constant supervision. He will pace for hours at a time, or he will wander out of the house repeatedly and get lost in his own neighborhood. These people are at risk for all kinds of accidents. They turn the stove on, and they forget to turn it off. They put their grandchildren's plastic pots on the stove and melt them and set fires.

They can become very, very suspicious, or what we would, as a layperson, call paranoid, or on the other hand, they may very injudiciously give away large amounts of money. They will be unable

to find their way around in their own neighborhood. They will be unable to find a bathroom in their family home.

They develop a language disorder, which is one of the major difficulties families face. As human, we communicate with each other, and as we gradually lose the ability to communicate with someone we love, the family suffers.

The patients develop difficulties dressing themselves and eventually will need to be completely dressed. Often, a son will find himself faced with the task of bathing his mother while she vigorously objects to that.

The patients will gradually lose the ability to walk. They lose the ability to remember anything. They will eventually lose control of their bowel and bladder functions. They may become completely confined to bed or to a chair. They will completely lose language and only make occasional cries or shout occasional words. They will eventually die of their disease.

The average course of the disease is 7 or 8 years, but often, these people will live for 15 years or more, which is a long time for a family to provide care.

There has been a pervasive myth in this country that Americans do not take care of their elderly, or that we dump them in nursing homes. There is very good data that indicates that that is absolutely not true, that Americans take very good care of these people. Better than half of the people with dementing illnesses, primarily Alzheimer's disease, are at home, being taken care of by family members, and that may be a spouse, himself suffering from chronic illnesses or a son or daughter, himself in his sixties, suffering from chronic illnesses. About 660,000 of these people live in nursing homes. The rest of those 1.5 to 2 million people are probably at home with their families.

However, there are changes in the American family that may make it increasingly difficult for someone to be home and to provide that constant, demanding kind of care.

We also know that, as far as we can tell, it is a very democratic illness. Alzhiemer's disease afflicts the very poor, the very wealthy, everybody in-between, of all races. Therefore, one finds people who have financial resources to seek help and families who are already struggling with a great deal of poverty and keeping someone home.

What is really amazing is that families in the face of the burdens they have are continuing to cope, continuing to find solutions, and continuing to be involved in voluntary associations such as the Alzheimer's Disease and Related Disorders Association. There are, of course, a few families who mistreat an Alzheimer's patient, as there are a few families who have difficulties in other areas of relationship. It is our clinical experience that when mistreatment occurs, it is almost always a result of the family's experience of fatigue, frustration, their lack of understanding of what they are up against, and their feeling of being totally isolated with this problem.

We have identified some areas in which we feel it is essential that families have resources if they are to continue to manage. Those areas are information, research, good medical care, symptom management skills, peer support, management of their own emotional distress, available and adequately funded respite care, ade-

quately funded long-term care when it is necessary, and equitable disability policies.

To meet these needs of the patient and families, we feel that five things are called for from the Congress: support of an ongoing research program, training for professionals, adequate alternatives to nursing home care, adequate and just funding of long-term care, and equitable disability policies.

Over and over, I am told that families do much better when they know what they are up against, and the organizations you have heard from have provided a very important lead in providing information for families, which has been extremely valuable to them.

Families need research as much as the rest of it. It is obvious that the staggering cost of caring for so many ill people is a justification in itself for research, but the research offers families their only hope, and it leaves them with the assurance that the Government is indeed committed to solving their problem, which is extremely important when you are living day to day with this issue.

Dr. Goldstein referred to the implications of the possible hereditary connection in Alzheimer's disease, and I also am not saying that it is a genetic disorder, but families need those answers, and they specifically need further research in that area.

Most important, perhaps, is the recognition that we can do a lot right now to make life easier for the family and for the patient. The patient's quality of life need not be awful. Not all of these patients are telling us that they are suffering and that they are miserable.

First of all, the family and the patient need to know that no treatable condition has been overlooked. About 10 percent, perhaps, of the people with a dementing illness do have a treatable condition.

I wanted to raise one cautionary issue about the diagnosis of Alzheimer's disease, which at present can only be made on examination of brain tissue. Alzheimer's disease as a term must not become a new wastebasket term that replaces senility or organic brain syndrome. As long as there are implications about its hereditary nature, we must not casually apply that diagnosis to anyone.

An important factor in the diagnosis is to identify what the patient can still do. Alzheimer's disease is not an all-or-nothing kind of loss. The patient still retains specific abilities, and when these are identified and spelled out for the families, they know what they can reasonably expect from a patient, and when their demands are making the patient worse because he cannot do something.

Patients with Alzheimer's disease quickly get much worse when they have some other illness—and that can be heart disease, or it can be something as mild as the flu. Good medical management of concurrent illnesses and other illnesses can help the patient to function at his maximum level and therefore make life much easier for the family. Whenever we see a patient suddenly get worse, we look to see what else might have gone wrong. Therefore, one of the most important issues for families is that physicians and nurses across the country be trained to look for and followup on these other illnesses that the Alzheimer's patient develops.

Good medical care remains difficult for families to find in many areas. However, that is changing. An important factor in the provi-

sion of good medical care is the realization that conditions like dementia call for a willingness to provide chronic rather than acute care. That is a kind of care in which the goal is to maximize a person's function rather than to provide a cure, until such time as a cure is available. This is a dramatic change in perspective for the public and for many physicians, and we feel that a strong lead is needed to call for the training of physicians, nurses, and all the other allied health professionals in this area.

The Alzheimer's Disease Association has been invaluable to families in letting them know that they are not alone with their problems, and in helping them to manage their own feelings of fatigue, anger, and depression at what they are dealing with. I want to emphasize the importance of the government's lead in establishing that organization.

The families who are providing care are doing so around the clock, and it is our clinical opinion that good respite care, alternative to the families doing it around the clock, is vital for their continued success. We feel that a range of respite care resources should be available—daycare, care in the person's home, foster care or boarding care facilities, periodic, temporary hospitalization, are some of the alternatives that should be equally available to families as long-term care. I want to emphasize that those respite resources are probably not a complete alternative to long-term care. The idea that they are an alternative to long-term care is based on our assumption that people dump their families in institutions. In fact, if the families do not get any help, they soldier on as long as they can, until they collapse. The human cost of doing that is staggering, especially if you consider that they may be doing this for as much as 15 years.

We feel that new policies, or changes in policies, are important. Medicare, for example, provides in-home health care only when the services of a skilled nurse are also needed. In-home care, someone to give the person a bath, help with feeding them, help get them up in the morning, are extremely important to the family, and such care needs to be available to them.

I have been very impressed in the last few months with what I have seen in daycare facilities, and here again, different kinds of funding and resources are called for. I see patients who look like life is better for them than when they are at home alone, or when they are in the typical nursing home. There is also some preliminary evidence that that kind of quality care keeps people on their feet until close to the end of their illness and avoids a long period of bed care, which is difficult for everybody and costly.

Brief hospitalizations are important. Every once in a while, a family just collapses. For example, there may be a new baby born in a family, or someone else has to have surgery, and at that point, a family needs to be able to briefly hospitalize the impaired person. Brief hospitalizations also give us a chance to carefully readjust a person's medications so that he is functioning at his maximum level.

It is difficult to make cost comparisons, as I say, between long-term care and respite care resources. The families know that if they have to pay respite care is a smaller out-of-pocket cost than their payment for long-term care. However, quality care and res-

pite care is often of a better quality than what a patient is getting in a nursing home, especially if he is getting medicaid assistance.

However, we believe that long-term care is a necessary alternative for some families at some point in the patient's illness. In some areas, nursing homes will not accept Alzheimer's patients. They are difficult people to take care of in a nursing home, as well as at home. In some places, funding policies have the effect of excluding Alzheimer's patients. In some cases, medical assistance policies require that the family member, particularly if it is a wife, must impoverish herself in order to obtain care, after she has done all that she can, as long as she can, for someone she loves.

Families tell us that they are not receiving equitable retirement and disability treatment. This is an area that needs further study and further understanding, so that we know what is going on. However, there is no doubt that Alzheimer's disables its victims as cruelly as any other catastrophic illness, and it is an illness, and that because it is a disease, its victims are entitled to appropriate retirement and disability income. This is particularly tragic when Alzheimer's disease strikes someone who is younger than the traditional retirement age.

In conclusion, then, most families are heroically fighting a devastating illness. Supporting them can be rewarding to professionals and, we believe, a legitimate goal of the Congress. We must be realistic and not oversell our ability to dramatically cut costs or dramatically and immediately resolve all problems. But we cannot turn our backs on the families of so many people.

Families and volunteer groups in the private sector are doing much. However, we feel that there are five things that are needed that need the leadership of the Congress: Ongoing support for research; support for the training of professionals at all levels, so that they can give adequate information, care and help to the families who consult them; provision of a variety of alternative respite resources so that the family can get a break; equitable funding for quality long-term care for those families at such time as it is necessary, and quality long-term care when it is required, and equitable disability policies.

Thank you for the opportunity to speak on behalf of all those families.

Senator GRASSLEY. Thank you.

[The prepared statement of Ms. Mace follows:]

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Coordinator of the T. Rowe and Eleanor Price TEaching Service
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Mr. Chairman, thank you for the opportunity to present the needs and concerns of families of persons with Alzheimer's disease.

I am an Assistant in Psychiatry at Johns Hopkins Department of Psychiatry and Behavioral Sciences at Johns Hopkins University and the Coordinator of the T. Rowe and Eleanor Price Teaching Service. We provide care for demented patients, teach their care to professionals, and conduct research into the needs of patients and families. I am also a member of the Board of Directors of the Alzheimer's Disease and Related Disorders Association. My testimony today is on behalf of The Johns Hopkins University.

I shall briefly describe the victims of Alzheimer's disease, discuss the characteristics of their families, and then discuss those things families need in order to provide good care to their loved ones.

The Victims

It has been estimated that between 2 and 3 million people in this country suffer from some degree of intellectual impairment.(1) At least half of these suffer from a disorder of the Alzheimer's type. A study of the epidemiology of mental health in the United States, funded by NIMH,(2) will soon give us a clearer understanding of the prevalence of this dementing illness in this country.

Alzheimer's disease is believed to be the 4th or 5th leading cause of death in this country(3) (data based on death certificates do not reflect this because death certificates often state as cause of death a secondary illness such as pneumonia or use a general term such as "organic brain syndrome"). We do know that the prevalence of Alzheimer's disease increases with age. Rare cases have been identified in people in their 20s and 30s. Less than 1% of the people in their 50s are afflicted. However, about 2% of people at age 65 and about 20% of people at age 80 are victims of the disease.(4) The over-75 age group is the fastest growing segment of the population.(5) Thus, unless a prevention or cure is found, the number of people with Alzheimer's disease can be expected to increase by 50% by the year 2000 (6). Since most elderly people have spouses (65%), children (80%), grandchildren and great grandchildren,(7) the impact of this disease stretches far beyond the victim.

Alzheimer's is a disease of incidious onset and devastating course. Its initial symptomis a loss of recent memory. Early in the course of the disease the patient is often acutely aware of his losses and may become depressed or anxious. Patients often lose their jobs or have several automobile accidents. The person often seeks to cover up his failures, and to his family he may only appear to be vaguely upset, discouraged or more irritable. As the disease progresses, the memory loss becomes more profound and the person will need constant supervision. These patients

often pace for hours or wander away from home and get lost. They are at risk for many kinds of accidents. They cannot live alone because they forget to feed themselves, take their medications or turn off the stove. They may become highly suspicious or injudiciously give away their money. The person may become unable to locate the bathroom in his own house or to find his way about in his own neighborhood. He may forget the names of his children and may not recognize his own spouse.

Alzheimer's victims develop a language disorder which makes it increasingly difficult for them to understand what is said to them or to communicate their needs and thoughts. They develop difficulties in coordination so that they gradually become unable to dress themselves or feed themselves without assistance. They develop a stooped posture and a shuffling gait. They may fall frequently. In the latter stages of the disease they will be unable to remember most things (when tested they will be unable to remember one word for one minute). They will lose control of their bowel and bladder functions and have significant difficulty in walking. They may become unable to walk and be confined to bed. They will become completely unable to communicate, and may produce only occasional words or cries.

The disease is inexorable and fatal. The average person will die 7 years after onset. However, the course is quite variable; in some people it will progress much more rapidly and many other patients linger for 15 years or more.

Throughout the course of the illness the impaired intellectual function often makes these individuals prone to irritability, stubbornness, argumentativeness, and sudden explosive bursts of temper. Alzheimer's victims may also become apathetic, unresponsive, depressed or moody.

The Families

The tragedy of a dementing illness is not limited to the patient himself. The patient's family suffers as well and has been called the "other victim of dementia." Although any chronic and fatal illness can have a tremendous impact on the family, the very nature of a brain disease adds significantly to the family's burden. Family members report the effects of the almost overwhelming burden of caring for a person with a dementing illness. They struggle to provide physical care, to find their way through often uninformed agencies, to accept the loss of communication, and changes in personality and to grieve as the patient gradually declines.

There is a pervasive myth in this country that Americans "dump" their elderly in long term care institutions. This has been clearly disproven by the work of Shanas(8) and Brody(9). Shanas has documented that American families live close to their elderly relatives and visit them often. She has further documented that the family supportive relationship has not

changed significantly over the past twenty years. E. Brody has shown that the elderly, the middle generation and the third generation of grandchildren believe that care should be provided by the family and that the family in fact does provide the majority of personal care, shopping, and even nursing care.

An analysis of data on the living situations of demented individuals(10) shows that approximately 660,000 of the demented are living in long term care facilities. A few live in boarding homes, hotels, or alone. The remainder, more than half, live with their families. Demented individuals who are in institutions as a group are older, more likely to be widowed or to never have been married, have fewer children and are sicker than those living with their families.(11) Thus, they are people who have fewer family members available to care for them and who need more skilled nursing care. Such data demonstrates that Americans do not abandon their elderly or dump them into institutions.

However, Brody(12) also points out changes in the American family. There are more women (the primary caregiver for the frail elderly) who are employed full time outside the home. There are more sons and daughters who are themselves aging and there are more single parent families. These changes may adversely affect the family's ability to provide care unassisted in future years.

Current evidence indicates that Alzheimer's disease is a democratic illness. It appears to equitably afflict people of all economic and social classes and all racial or national origins. Thus one finds the families of Alzheimer's disease to be among the desperately poor, among the very affluent and among the middle classes. One finds family members to be spouses who are themselves elderly and suffering from chronic illnesses. The restricted means imposed by retirement and the limited mobility common in the elderly compound the demands of care. One finds sons or daughters themselves in their 60s who may also have responsibility for an aging spouse, adult children and grandchildren. One finds family members who have children in the household. When Alzheimer's disease strikes its victim early, one finds adolescents struggling to accept this devastating illness in a parent.

To determine the impact of a dementing illness on the family caregiver we looked at a group of families caring for demented patients. We asked them what behaviors caused problems for them. The results are reported in the attached article by Rabins, Mace and Lucas.(13) Common problems (reported by more than half the families) include the patients who exhibited explosive irritability, anger or demanding or critical behavior; patients who were awake and active at night (When the patient is up at night, the caregiver must be awake also, to insure that the patient will not wander away or start a fire. We find chronic lack of sleep to be devastating for caregivers). Many families had significant difficulties in communicating with the

patient,reported patients who were inappropriately suspicious or "paranoid", patients who unjustly accused family members of stealing their things, patients who wandered out of the house and got lost, and patients who refused assistance with baths. Incontinence, physical violence, unsafe driving, behaviors causing fire hazards and hallucinations were also reported. The majority of families reported struggling daily with many of these problems. The length of this list of difficult behaviors is indicative of the burden faced by caregivers.

We also asked these caregivers about the problems they themselves experienced as a result of caring for the ill person. This data is discussed in the same article. Most of the families reported experiencing chronic fatigue, anger and depression. Many of them found themselves in disagreement with other family members. More than half of the caregivers had had to give up friends and outside interests and had no time for themselves as a result of their caregiving roles. They worried that they themselves would become ill and that there would be no one to care for the impaired person.

Other researchers have found similar stresses in families caring for demented or brain-injured adults. Lezak(14) describes families of brain-injured adults as feeling frustrated, trapped, isolated, abandoned by the extended family and sometimes abused by the brain-injured patient. She identifies the special problems of the spouses whose sexual and affectional needs are frustrated and who cannot properly mourn the loss of the person who has changed so drastically and yet who remains alive. To translate this data into human terms let us consider a typical family who turned to Johns Hopkins for help.

> "My father is 64 and has hypertension. He has to watch my mother all the time. She gets up at night, gets dressed, turns on the water and opens the front door. He cannot leave her during the day even long enough to go to the grocery store. She turns on the stove and we are afraid she will start a fire. She accuses him of stealing her things and says he is not her husband. I do all I can to help but I have three small children and a full time job. It takes my father, my oldest daughter and myself to give her a bath."

In light of all these problems the truly amazing thing is that most families soldier on and find creative methods of surviving and caring for their ill family member. The majority of families are successfully helping themselves. It must be emphasized that most of these caregiving families are not disturbed or pathological families. The majority of families have a lifelong history of coping skills upon which they can draw to solve the difficult problems of a dementing illness.

Of course there are some families who abandon, abuse, or

mistreat the demented elderly person. There are some families who are unable or unwilling to understand and accept the nature of the person's cognitive impairment and there are some families who take financial advantage of the cognitively impaired person. Our clinical experience is that abuse, when it does occur, is often the result of fatigue, frutration, lack of understanding, and a sense of isolation.

However, the long term demanding nature of Alzheimer's disease can exhaust a family's emotional, physical and financial resources, thus devastating the family as well as leaving patient unsupported. It is important to identify what a family must have in order to continue to provide care for their ill member.

Needs

We have identified the areas in which adequate support and resources are required if families are to successfully provide long term care: information, research, good medical care and symptom management, peer support and management of emotional distress, available and adequately funded respite care, available and adequately funded long term care, and equitable disability policies. The ideal for the family would be a coordinated effort, involving the family and community, the private sector and the government. The theory has been put forward that when formal supports become available, the informal or self-help system is less effective. Other authors(15) contend that exactly the opposite occurs. They argue that adequate formal supports enable a family to continue to function and provide care to its impaired member. Our clinical experience bears this out. Clearly many of the needs of families are met by informal systems, particularly the dissemination of information, peer support, management of emotional distress and the acquisition of symptom management skills. However it is equally clear that only the Congress has the ability to generate change in areas such as research, improved medical care and funding incentives for quality care.

To meet the needs of patient and family five things are called for:

1. an ongoing research program
2. training for professionals
3. adequate alternatives to nursing homes
4. adequate and just funding of long term care
5. equitable disability policies.

Good care is not cheap: good programs cost money. For example, it will cost the family the same amount to see a physician who will tell them that their loved one is senile and that nothing can be done or to see a physician who will tell them that the patient probably has Alzheimer's disease but that much can be done to improve the quality of life for patient and the family. The first physician may not see his patient again for a

year at no dollar cost. The second physician will see his patient again at least once and spend time on the telephone carefully titrating medication so that the patient - and family - can sleep at night.

A. The Family's Need for Information.

The dementing illnesses have been much misunderstood. Few other illnesses are surrounded by so much commonly held misinformation. Many individuals still believe that "senility" is the inevitable fate of anyone who grows old. In addition, the behavior of a person with Alzheimer's disease can seem to the uninformed to be angry, purposefully nasty or frightening. The loss of abilities and changes in personality in the absence of an understanding of their causes have often been interpreted as "psychological", or "neurotic" or within the control of the individual.

The lack of community understanding of dementia limits the community's acceptance of aberrant behaviors and restricts approbation of the family's coping strategies, thus further isolating the caregiving family.

The Family Survival study(16) found that "access to information, advice and referrals...is a priority need for victims of organic brain damage and their families...". Families need information about the nature of the disease, its etiology, its progression, how to care for the patient and what plans needs to be made for the future. Families need to be aware of the financial realities of professionally provided care and be encouraged to plan ahead.

The last 5 years have seen a rapid expansion in the available information about the dementing illnesses in general and in particular about Alzheimer's disease. The literature disseminated by the NIH, particularly "The Dementias, Hope Through Research, NIH No. 81-2252(17) and Alzheimer's Disease, Q & A, NIH No. 80-1646(18) has made a significant improvement in public understanding. Countless families have given their physician the pamphlet, Alzheimer's Disease, A Scientific Guide for Health Practitioners, NIH No. 81-2251.(19) This, combined with the efforts of private individuals and organizations such as the Alzheimer's Disease and Related Disorders Association, has vastly improved public understanding of this widespread disease.

B. The Family's Need for Research

You have heard from other witnesses of the importance of an ongoing effort in basic research to identify causes, potential treatments or cures for this devastating disease.

Clearly the staggering cost of caring for a growing population of Alzheimer's disease victims is in itself sufficient justification for a vigorous search for cause and treatment. The

estimated cost of nursing home care for demented individuals in this country in 1982 was 13 billion dollars. In 1990 the projected cost will be 38 billion dollars.(20) This figure refers only to the approximately 1/3 of these victims who use institutional care. The cost of the victim's lost wages, or those of a family member who provides full time care, the cost of in-home care services, respite care and medical care are not included. Neither are the emotional and psychological costs the family included in these estimates.

In addition to its primary goals, which the other witnesses have ably outlined, ongoing research offers families their only hope. The significant advances in research in the past decade are a source of comfort to families. Information about current research gives them both realistic expectations and reassurance that the nation understands their needs. Many families tell us that participation in research programs gives them some sense of control over a currently incureable illness.

The work of Folstein (21) and others indicates that Alzheimer's disease may be a hereditary condition. The implications of such findings have an impact on all family members. Further research is needed to clarify this issue.

Families who have watched their loved one decline over many years desperately seek any and all help. Thus, they are vulnerable to "quack cures." They need instead a vigorous research program which will rule out dubious treatments and instead describe the etiology, epidemiology, potential treatments and potential cures for this illness.

C. The Family's Need for Good Medical Care and Symptom Management

1. Diagnosis and Evaluation

The family needs an accurate diagosis of the patient's condition. About 10% of the patients seen in most clinical evaluation settings are found to have a treatable or potentially reversible dementia. A thorough diagnosis reassures the family that no treatable condition has been overlooked and defines the patient's distressing behaviors as medical rather than a "psychological" or "caused by something the family did."

One caution needs to be mentioned with regard to diagnosis. Alzheimer's disease must not replace "organic brain syndrome" as a wastebasket term for all dementias of unknown etiology. As long as the possibility of a hereditary factor in Alzheimer's disease remains, this diagnosis affects both the patient and subsequent generations. Such a diagnosis must be made judiciously and only after a complete evaluation has ruled out any other possible cause.

A thorough evaluation helps the family and the clinician

identify areas of spared and impaired function so that realistic expectations of the patient's remaining degree of independence can be established.

2. Symptom Management

Many of the behaviors which families find overwhelmingly difficult are brought on not by the dementing illness but by a confused state (delirium) or a concurrent illness. These have been shown to respond to appropriate medical interventions with subsequent improvement in behavior.(22) For example, incontinence may be the result of a urinary tract infection, prostate disease or a gynecological problem. Incontinence, when it occurs, can be so distressing for the family that some authors have felt that it is a major precipitant of institutionalization. However, it is our clinical experience that treatment of the underlying disorder frequently reduces or postpones the onset of incontinence.

Night waking and agitation both can overwhelm and exhaust the caregiver. Both are responsive to the combined interventions of environmental adjustments and the judicious use of medication. Thus, a search for a cause or causes of behavior change and a cautious tinkering with the patient's status can have a significant impact upon the family function.

A study(23) of patients living in long term care facilities showed that as many as one quarter of them have other undiagnosed or incompletely treated conditionswhich compound their cognitive impairment. Such patients have been shown to improve when these conditions are appropriately treated. This further supports the argument for good, ongoing medical care.

An important aspect of family success in caregiving is the mastery of skills in managing or reducing those patient behaviors which are frustrating, exhausting or life threatening. THE 36-HOUR DAY (24) (which has been made available to your staff) deals at length with symptom management skills. However, what the family learns from any book or any organization may be much less useful to them than information received from the physician and other health professionals who know the patient, whom they trust, and who can tailor these principles to individual needs. It is imperative that professionals be well trained in symptom management skills.

3. Availability of Good Medical Care

Families provide most of the day to day care of these patients but they need the reassurance that professional help is available for them when needed. Good medical care remains difficult for families to find in many areas. However, this is changing as more physicians learn that they can make significant interventions in these cases, leading to improved patient well being.

A 1981 Rand Corporation study indicated that by 1990 we will need between 7,000 and 10,300 geriatricians.(25) However, at present many physicians are not expert in the care of the Alzheimer's victim. Further, conditions like dementia call for a willingness to provide chronic rather than acute care, that is, care in which the goal is to maximize function ratherthan to obtain a cure. This is a dramatic change in perspective for the public and for many physicians.

It is not just to physicians that families turn for assistance. The care and management of a demented individual often requires the skills of allied health services. Care of the demented person in long term care is primarily in the hands of nurses; much community care is also provided by nurses. Families turn to social workers and psychologists for assistance in unraveling family problems, financial problems and to assist in the search for resources. The occupational therapist is trained to review the patient's ability to care for himself and to devise ways to maintain independent function. Health professionals must clearly understand the nature of Alzheimer's disease if they are to assist the family effectively.

Funds are needed to encourage geriatric training in all health fields, including medicine, and to encourage the continuing education of professionals now in practice.

I am here today because I wrote a book, The 36-Hour Day, for families on the management of people with dementing illnesses. It was possible for me to write this book because I am employed at Johns Hopkins under a private endowment by the T. Rowe and Eleanor Price Foundation. When a member of Mr. Price's family became ill, he, despite his financial resources, had difficulty in finding doctors and nurses who were knowledgeable about the ongoing care of Alzheimer's patients. He therefore turned to Johns Hopkins University to "teach doctors and nurses the care and management of demented patients". When such a resourceful individual has difficulty finding what he needs, one can only imagine the difficulties of the average person who must thread his way through endless referrals and encounter those who know nothing, and those who give bad information ("nothing can be done, he is only senile"). This inadequacy and unavailability on the part of the professional community can be the final blow which overwhelms the family.

D. The Family's Need for Peer Support and Management of Emotional Distress

Many families are experiencing emotional distress: grief, depression, anger, guilt and the loss of friends or outside interests in addition to providing 24-hour-a-day care and supervision. These emotions are compounded by lack of information, isolation, and fatigue. Sometimes these distressing emotions contribute to certain responses which makes the patient

less manageable.

Studies of distressed individuals seeking help shows that the majority of people spontaneously seek help from the informal support network which includes the extended family, friends, clergy, supportive counseling and self-help groups.(26)

The importance of self-help groups for families is perhaps best demonstrated by the rapid development and expansion of the Alzheimer's disease and Related Disorders Association which was initiated through the efforts of Marian Emr and Robert Butler at NIA in the fall of 1979. This organization now has 68 chapters and 300 support groups. Such voluntary support groups represent one of the ways in which assistance comes to families through resources other than government.

E. The Family's Need for Available and Adequately Funded Respite Resources

Caregivers often devote long days to providing supervision or nursing care. As they give up other activities, they become isolated and exhausted. It is our clinical opinion that appropriate supportive services may help to prevent premature institutionalaization, over-use of emergency medical services and family burnout. We believe that periodic respite from care is a critical element in a family's continuing ability to keep a patient at home as long as possible although there is no research data to date to prove this. The theory that respite care will prevent institutionalization is based on the belief that families "dump" patients in nursing homes. There is evidence that even when families do not have adequate resources they keep the patients at home as best they can as long as they can. However, the human cost may be exorbitant.

Ideally respite resources should be available in a variety of forms so that a family can select that which is most appropriate to their needs or most appropriate at a specific point in the course of the patient's illness.

Respite resources ideally would include in-home help, adult day care and periodic inpatient care and foster (or board and care) homes. The Family Support study(27) states that "In home supportive services for families of adults with chronic organic brain disorders or damage reduce the need for institutionalization as long as acute physical illness and/or deterioration does not require hospitalization or other 24 hour medical care" and "provision of services to families of adults with chronic brain disorders is a cost effective approach of care and assistance."

Excellent models for respite resources exist. However resources are frequently not available or families may not be able to afford them. Often funding resources and policies have the effect of excluding Alzheimer's patients from utilization of

existing resources or the resource is not prepared to accept these difficult individuals.

1. In-home Care

Medicare policy (28) provides in home health aide services (a person who will assist with bed care, personal care, bathing, feeding) when the services of a skilled nurse are needed to manage an acute or unstable medical condition or to periodically reassess the patient's medical status can be justified. Many families desperately need the services of an in home health aide but because the chronically ill are excluded from receiving it under Medicare. Medicare briefly permitted the services of an occupational therapist as a primary service, but rescinded this policy (29). The skills of an occupational therapist are often very useful to the family seeking to maximize patient function.

Many such families are forced into a revolving door kind of service utilization in which they struggle as best they can to provide constant supervision and personal care to a impaired person. When they are unable to meet a patient's care needs, when the patient developes another illness or when the family collapses from exhaustion the patient, emergency medical care is sought. Acute interventions are paid for by Medicare until the patient's situation restablizes. The family is then denied further services and struggles on until the system again collapses. Such cycles contribute to the family's demoralization.

2. Day Care

A few day care centers are serving the severely demented elderly. Day care offers the opportunity for the family to periodically get away from the impaired person to visit with friends, do the shopping, or attend to personal needs. Such activities are essential if the caregiver is to successfully continue to provide care.

After observing day care centers throughout the United States I am impressed by the appearance of the Alzheimer victim in these programs. It appears that the opportunity to function in a social setting with other individuals who are similarly afflicted is a benefit to the Alzheimer's patient. There is some evidence (James Haycox, private communication) that such facilities prevent or postpone the time in which the Alzheimer's patient becomes bed ridden and needs skilled nursing care.

3. Foster Care

Foster care (or board and care services) are yet another viable option which permits the patient to live in a home-like setting when the caregiver is himself ill or must be employed.

4. Brief Hospitalization

Occasional brief hospitalizations may allow the family periods of respite during which they can stabilize a family crisis or take a much needed vacation. (It must be emphasized that a vacation for a family may not be a luxury. It may be an essential opportunity to regain their mental health so that they can again assume the burden of patient care.) Periodic temporary hospitalizations allow the opportunity for close observation of a patient whose medications need careful titration. Acute care facilities with all their attendant equipment and highly skilled staff are sometimes used for this purpose. Less highly specialized facilities may be less costly and equally appropriate.

It is difficult to make comparisons of the cost of long term care and alternative respite resources. In general, alternative respite resources require a smaller out of pocket expenditure for the family than the burden of nursing home care. However, this does not take into account lost wages, quality of life for either patient or family, transportation, medical care costs and so forth. Good cost comparative studies and studies of whether respite postpones institutionalization have not been made and are called for.

I asked the director of a study which is designed to include cost comparisons, what her findings are. She replied that "we are only beginning to analyse the data, however it appears that, when all the hidden costs have been factored in, our respite program may be close to the cost of long term care, but infinitely more humane".

Quality care, then, is not cheap. However, when we compare an excellent in-home service, day care program, or foster care program to the kind of nursing home care available to most demented people, several other factors emerge.

The first is the quality of care. In many nursing homes not only is the patient deprived of his family relationsnips, his privacy and his home surroundings, he will infrequently see a physician and only very limited nursing and social work skills will be available to him. He may be over-medicated, not treated for other illnesses, under-stimulated and confined to bed or geri-chair. In contrast, the respite programs which may ultimately be found to cost nearly as much, provide excellent physicians, nurses, social workers and rehabilitation therapists. The patient's familiar setting is emphasized, minimal medication is used, he is encouraged to remain mobile, and he is offered social companionship.

F. The Family's Need for Available and Adequately Funded Long Term Nursing Home Care

We believe that nursing homes are a necessary alternative in the long term care of the demented person.

In some areas nursing homes will not accept Alzheimer's patients, leaving the family with no choice except the dismal locked wards of a mental institution. In others, care is inadequate to the needs of the demented. Adequate funding, staff training, and policy changes are needed to insure that Alzheimer's victims are accepted and receive good care.

A major funding source for the care of Alzheimer's patients in long term care is the Federal Medical Assistance Program.

Medical Assistance policies may require that a family impoverish themselves in order to obtain necessary 24 hour skilled nursing care for a loved one. Families may be forced to keep a patient at home long past the time when the family's care is appropriate or adequate. The trend toward further restrictions on funding for nursing home care (which cost from $14,000 to $22,000 or more per year) will impose severe burdens on families who have already done all they can emotionally, physically, and financially - often for many years - for a demented loved one.

When the husband has been the primary wage earner and most of the family's income and assets are his, the wife may find herself financially dependent upon him. If it is he who becomes ill and in need of medical assistance payments she may be left so impoverished that she cannot even afford carfare to visit him or adequate care for herself.(30) This policy is both discriminatory and destructive as it contributes to the decline of the wife's health and well being, leading to her increased dependence upon public funds for physical care, transportation and social support services.

G. The Family's Need for Equitable Disability Policies

When Alzheimer's disease strikes a person under 60 or under 65 the family may find themselves unable to obtain disability or retirement benefits. The nature of a dementing illness is such that the extent of the patient's disability may not be evident by traditional assessment methods. Many families have complained to us that they were denied retirement or disability benefits appropriate to the patient's degree of impairment. This is a multifaceted problem and one which has not been adequately explored. However, there is no doubt that Alzheimer's disables its victims as truly as any other catastrophic illness and that, because it IS a disease, its victims are entitled to appropriate retirement or disability income.

Summary

In conclusion, most families are heroically fighting a devastating illness. Supporting them can be rewarding to professionals and, we believe,a legitimate goal for the Congress. We must be realistic and not over sell our abilities to dramatically cut costs or resolve problems, but we cannot turn

our backs on the families of 2-3 million people. Families and volunteer groups can do much for themselves, however five things need the leadership of Congress.

1. Ongoing support for research
2. Support for training of professionals
3. Provision of a variety of alternatives respite resources
4. Equitable funding for quality long term care when it is necessary
5. Equitable disability policies

(References will be forwarded by 5/20/83)

REFERENCES

1. Blessed, G., Tomlinson, B. E., Roth, M.: The Association Between Quantitative Measures of Dementia and of Senile Changes in the Cerebral Gray Matter of Elderly Subjects. British Journal of Psychiatry, 114: 797-811, 1968.

2. Epidemologic Catchment Area Studies in Baltimore, New Haven, St. Louis, Durham and Los Angeles.

3. Katzman, R.: The Prevalence & Malignancy of Azheimers Disease: A Major Killer Arch Neurol, 37: 217-218, 1976.

4. Kay DWK, Beamish D., Roth, M.; Old Age Mental Disorders in New Castle Upon Tyne. British Journal of Psychiatry, 110: 146-158, 1964.

5. Blessed, G., Tomlinson, B. E., Roth, M.: The Association Between Quantitative Measures of Dementia and of Senile Changes in the Cerebral Gray Matter of Elderly Subjects. British Journal of Psychiatry, 114: 797-811, 1968.

6. Kramer, M.: The Increasing Prevalence of Mental Disorders; Implications For the Future. Read Before the National Conference on the Elderly Deinstitutionalized Patient in the Community. Arlington, VA May 28, 1981.

7. Shanas, E.: The Family As A Social Support System In Old Age, The Gerontologist, 19: 169-183, 1979.

8. Shanas, E.: The Family As A Social Support System In Old Age, The Gerontologist, 19: 169-183, 1979.

9. Brody, E.: Aging & Family Personality: A Developmental View, Family Process, 13: (1) 23-37, 1974.

10. Brody, E.: The Formal Support Network: Congregate Treatment Settings for Residents with Senescent Brain Dysfunction, Miller N., Cohen, G., Clinical Aspects of Alzheimers Disease and Senile Dementia, Raven Press, 1981.

11. Ibid.

12. Brody, E.: "Women In Middle" and Family Help to Older People, The Gerontologist, 21: (5) 471-479, 1981.

13. Rabins, P. V., Mace, N. L., Lucas, M. J., The Impact of Dementia on the Family, JAMA July 16, 1982, 248: (3) 333-335.

14. Lezak, M.: Living With the Characterologically Altered Brain Injured Patient. Journal of Clinical Psychiatry, 39: 592-98, 1978.

15. Zarit, S. H., Relatives of the Impaired Elderly: Correlates of Feelings of Burden, Gerontology, 20: 649-655, 1980.

16. Final Report of Bridges to Survival, A Project to Assist Families in Securing Services, Information and Counseling Necessary for the Care of Brain-Damaged Family Members. July, 1981. Family Survival Project, 1736 Divisadero St, San Francisco, CA 94115.

17. The Dementias, Hope Through Research, NIH #81-2252

18. Alzheimers Disease, Q & A, NIH #80-1646.

19. Alzheimers Disease, A Scientific Guide for Health Practioners, NIH #81-2251.

20. HCFA - Projected National Health Expenditures 1990

21. Folstein M., Breitner J.: Language Disorder Predicts Familial Alzheimers Disease, Johns Hopkins Medical Journal, 149: 145-147, 1981.

22. Snyder, B., Harris, S.: Treatable Aspects of the Dementia Syndrome, Journal of the American Genatic Society, 24: 179-183, 1976.

23. Sabin, T., et. al., Are Nursing Home Diagnosis and Treatment Inadequate?, Journal of The American Medical Association, 248: 321-323, July, 1982.

24. Mace, N. L., Rabins, P. R., The 36-Hour Day, A Family Guide to Caring for Persons with Alzheimer's Disease, Related Dementing Illnesses, and Memory Loss in Later Life, Baltimore, John Hopkins University Press, 1981.

25. Kane R. L., et. al: The Future Need for Genetic Manpower in the U.S., New England Journal, 302: 122-132, 1981.

26. Caplan G.: Mastery of Stress: Psychiatrical Aspects, American Journal of Psychiatry, 138: 413-20, 1981.

27. Final Report of Bridges to Survival, A Project to Assist Families in Securing Services, Information and Counseling Necessary for the Care of Brain-Damaged Family Members. July, 1981. Family Survival Project, 1736 Divisadero St, San Francisco, CA 94115.

28. Medicare, Your Medicare Handbook.

29. HCFA Legislature Summary 8/26/81 p. 5.

30. Caplis, J. W., Financial Effects of Nursing Home Placement on the Community Spouse 8/80.

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The Impact of Dementia on the Family

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• **To determine the impact of dementia on the family, we interviewed the primary care givers of 55 patients suffering from an irreversible dementia. Problems reported included disturbances of patient behavior such as catastrophic reactions, waking at night, suspiciousness, and communication disorders, some of which can be alleviated by physician-initiated intervention. Care givers also reported that they themselves had feelings of anger, depression, and fatigue, which can be treated as well.**

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THE DEMENTING illnesses are increasing in prevalence and present a major public health problem for the upcoming decades. Currently, they affect between 2 and 4 million people in the United States, and this number will increase by 50% during the next 25 years unless major advances are made in prevention and treatment of these illnesses.[1]

The majority of demented and frail individuals are cared for by family members in the home, not in institutions.[2] These families and patients often turn to physicians for evaluation, advice, treatment, and support.[3] This article reports the results of a study that sought to identify the problems for which such families are seeking help. The results identify the families' perceived needs and suggest interventions that physicians can make to lessen the burden placed on families by dementing illnesses.

METHODS

The families of 55 patients with diagnoses of irreversible dementia were surveyed. All were inpatients or outpatients in The Johns Hopkins University Department of Psychiatry, Baltimore, and fulfilled *Diagnostic and Statistical Manual of Mental Disorders III* criteria for dementia. They received clinical diagnoses of Alzheimer's disease (60%), multi-infaret dementia (18%), or other causes (22%). This is similar to the distribution reported in several other series of demented patients.[4]

The family member interviewed was the primary care giver, ie, the person with whom the patient lived or spent most of his time. For the three patients living in a nursing home and the five patients living alone, we interviewed the family member providing the most support to the patient. A structured interview was administered. This consisted of 52 questions examining patient behavior as well as problems the family member might be experiencing as a result of caring for the patient. Each question concerned a situation that was rated on a four-point scale—not occurring, occurring occasionally but not a problem, occurring sometimes and causing problems, and causing serious problems.

Thirty-nine of the patients were women and 16 were men. More of the women were widowed (51% of women *v* 6% of men; $P<.01$). Almost half (45%) of the patients lived with a spouse or a spouse and child. Half lived in other settings—with a child (16%), alone (9%), in a nursing home (5%), or with another relative, a friend, or a paid caretaker (the latter three, 23%).

RESULTS

Families were first asked an open-ended question: "What is the biggest problem you have in caring for the patient?" Twenty-two different problems were identified, which emphasizes the differences in patients and family systems and the importance of assessing each family individually. Three families denied having any problems.

Table 1 gives the responses to the questionnaire. Catastrophic reactions are the second most commonly occurring problem, preceded only by memory problems that are definitive for the condition. Catastrophic reactions were defined by Goldstein[5] as substantive emotional reactions precipitated by task failure. They can be as minor as an outburst of anger or as serious as a physical blow in response to a request to do something. A number of behaviors and feelings, including anger, crying, resistance to care, and arguing, were subsumed under this heading when it appeared that they derived from stress or task failure. A long list of other behaviors, including night waking, communication difficulties, suspiciousness, and wandering, seriously affect many of the responding families.

The "most serious" problems faced by families are presented in Table 2. The rank order is notably different from the order of problems by frequency. For example, violent resistance to care was reported in fewer than half of the patients, while hitting occurred in one third. However, both are usually very serious when they do occur. Incontinence occurred in 21 of the patients and was usually a major problem when present.

The problems care givers themselves experienced are presented in Table 3. Forty-eight care givers reported feeling angry, sad, depressed, or tired most of the time.

Also reflecting the substantive impact of these illnesses on the care giver is the finding that 30 of the respondents had given up friends, hobbies, or jobs or felt they had little or no time for themselves. Thirty-one care givers reported that they felt that other family members were not helping enough or were critical of the care they were providing, indicating the presence of family conflict. Role changes were reported as a potential source of distress by those who

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Table 1.—Behavior Problems of Patients Cited by Families

Behavior	No. of Families Responding*	Families Reporting Occurrence, No. (%)	Families Reporting Behavior to Be a Problem, No. (%)
Memory disturbance	55	55 (100)	51 (93)
Catastrophic reactions	52	46 (87)	40 (80)
Demanding/critical behavior	52	37 (71)	27 (73)
Night waking	54	37 (69)	22 (59)
Hiding things	51	35 (69)	25 (71)
Communication difficulties	50	34 (68)	25 (74)
Suspiciousness	52	33 (63)	26 (79)
Making accusations	53	32 (60)	26 (82)
Meals	55	33 (60)	19 (58)
Daytime wandering	51	30 (59)	21 (70)
Bathing	51	27 (53)	20 (74)
Hallucinations	49	24 (49)	10 (42)
Delusions	49	23 (47)	19 (83)
Physical violence	51	24 (47)	22 (94)
Incontinence	53	21 (40)	18 (86)
Cooking	54	18 (33)	8 (44)
Hitting	50	18 (32)	13 (81)
Driving	55	11 (20)	8 (73)
Smoking	53	6 (11)	4 (67)
Inappropriate sexual behavior	51	1 (2)	0 (0)

*"Don't know" answers excluded.

Table 2.—Behaviors Cited as Causing Serious Problems

Behavior	No. of Families Reporting It as Occurring	No. (%) of Families Reporting It as a Serious Problem
Physical violence	23	18 (78)
Memory disturbance	57	35 (88)
Incontinence	21	13 (62)
Catastrophic reactions	46	25 (54)
Hitting	18	8 (80)
Making accusations	32	16 (50)
Suspiciousness	33	16 (48)

reported having to assume responsibilities that had been the patient's. Respondents also reported feelings of guilt, worry, fear of illness, fear of the patient, and marital stress.

COMMENT

These findings show that the families of demented individuals who seek medical care face a large number of problems relating to the patient's behavior and mood. At the same time, the care givers themselves are experiencing the emotional and physical burdens of the care-giving role. Many families seek the assistance of physicians to alleviate or eliminate such burdens.

While some symptoms, such as memory loss, have no known treatment, many of the behaviors that the families cite as distressing are responsive to multifaceted intervention through environmental modification, good medical care, pharmacotherapy, and family education. For example, the frequency and impact of catastrophic reactions can often be lessened by teaching the family to avoid or remove the precipitating task or stress, to remain calm, and to change gently the focus of the interaction. Neuroleptic drugs are occasionally useful but only as an adjunct to these techniques. Hitting and violent resistance to care are extreme catastrophic reactions and often can be eliminated or lessened in severity and frequency in these ways. While communication disorders are not in themselves treatable, families can be taught techniques to improve communication and to reduce consequent catastrophic reactions.

Waking at night is a frequent and serious problem, because it deprives the care giver of much-needed rest. A variety of environmental interventions, such as keeping the patient physically active during the day and not allowing him to nap, may help him sleep better at night. Sedative-hypnotics or neuroleptics may occasionally be necessary.

Table 3.—Problems Care Givers Cite for Themselves (n=56)

	No.	%
Chronic fatigue, anger, depression	48	87
Family conflict	31	56
Loss of friends and hobbies, no time for self	30	55
Worry that care giver will become ill	17	31
Difficulty assuming new roles and responsibilities	16	29
Guilt	14	25
None	4	7

Suspiciousness and accusatory behavior caused serious problems for almost two thirds of the families. Pointing out that these behaviors are the brain-injured person's effort to explain misplaced possessions or misinterpreted events may reduce the anger and frustration the family feels in response to such behaviors. A simple environmental intervention, such as keeping an orderly house or making a sign pointing to where an object is kept, may help. Neuroleptic drugs occasionally decrease suspiciousness but, in our experience, often do not. We use them only when other approaches have failed, and the symptom is a major source of distress.

Incontinence is a major problem. The dementing illness may not be the cause of the incontinence, and its seriousness warrants a careful search for other causes, such as urinary tract infection.

Many behavioral problems worsen if the patient experiences a superimposed illness. Careful medical management of coexisting conditions, such as congestive heart failure and diabetes, aids the family by maximizing the patient's functioning. Even a minor illness, such as an upper respiratory tract infection or urinary tract infection, can worsen behavior. Because delirium is a common side effect of medication, close supervision of drug intake is also important.

Three potentially dangerous activities—cooking, driving, and smoking—are attempted by many patients. The distressed family may not recognize these or other potential hazards, such as firearms in the home. Physicians need to be alert to these situations and to assist the family in responding to them. Environmental modifica-

tions, such as removing stove knobs, locking rooms or closets, or locking up matches, are important for safety. Patients will often stop driving on orders of their physician. If not, the state motor vehicle bureau should be contacted.

Inappropriate sexual behavior, although often feared in the so-called senile, is rarely complained of by these families. This information can be reassuring to the families who fear this complication.

The validity of these results is supported by similar findings of other authors. Lowenthal[7] found that disturbances in thinking and feeling, potentially harmful behavior, odd behavior, and restlessness were the most frequent precipitants to psychiatric hospitalization of impaired elderly. Grad and Sainsbury[8] reported that families who cared for impaired elderly had more neurotic symptoms, less social activity, and more disrupted household routines than did a control group, while Sanford[9] found that families reported lack of time for themselves and sleep disturbances in patients as the least tolerable aspect of home care. The present study adds to such general observations specific behaviors that the authors have found responsive to intervention. It also suggests that interventions that decrease problem behaviors in the patients and provide some relief from care provision by family members have an important place in the care of the demented patient.

There are limitations to this study: interviewed families were seeking medical help and, therefore, might have been experiencing more problems than families who did not seek help. Also, using a structured questionnaire listing the many problems known to occur probably elicited more complaints than would have been obtained in an open-ended interview. Finally, since the questionnaire asks for the family's perception of problems, we may have elicited reports of behaviors we could not see clinically or negative answers to problems we would see. Our clinical impression was that this occurred infrequently. There are strengths to the approach used here, however. Most important, the use of a standardized structured interview has enabled us to determine the prevalence, severity, and impact of specific problems. Because such information identifies the patient behaviors and family-member needs that are most common, it can point toward those areas in which efforts to develop effective interventions could be most efficiently focused.

It is clear that the dementing illnesses have a notable emotional impact on families who seek help. We found that families had difficulty differentiating between feelings of anger, sadness, depression, and fatigue. This is similar to Parkes'[10] findings that these feelings states coexist during grief.

If, in fact, some of the problems most burdensome to the care givers of demented patients are amenable to social, psychological, and pharmacological interventions already available, we should be able to demonstrate a decreased morbidity in families after such interventions have been made. There are no published studies we know of that support such a conclusion, but Bergmann et al[11] have found that "family support" was the major variable in keeping the cognitively impaired elderly at home. Zarit et al[12] have recently found that the lowest "burden" ratings reported by the families of demented community-residing individuals were found in the families receiving the most frequent visits from others. This hypothesis is also supported by Caplan's[13] findings. He reviewed studies of stress intervention and concluded that the vulnerability to illness of the individual under stress may be reduced if he receives social support in mastering the stressful situation.

Finally, since family members find the lack of relief from care giving and chronic fatigue to be major sources of distress, we believe that relief services, such as home health aids and brief hospitalizations, may increase the family's ability to care for the cognitively impaired at home, lessen the difficulties they face, and help keep down rapidly escalating nursing home costs. This hypothesis also needs further study.[14]

While we recognize that some symptoms of dementia—for example, memory loss and communication disorder—are not reversible, we have identified behavioral problems in demented patients and emotional and physical burdens of their caretakers that can be lessened with our current knowledge. Our clinical experience indicates that an individually tailored care plan that includes support and education for the family, support for the patient, utilization of community resources (such as visiting nurses and day-care centers), environmental changes to reduce catastrophic reactions, optimization of the patient's medical status, and pharmacological interventions for behavioral problems does assist families in meeting the demands of these illnesses.[15,16] It remains for further studies to validate this contention.

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References

1. Kramer M: The increasing prevalence of mental disorders: Implications for the future. Read before the National Conference on the Elderly Deinstitutionalized Patients in the Community, Arlington, Va, May 28, 1981.

2. Kay DWK, Beamish P, Roth M: Old-age mental disorders in Newcastle upon Tyne: Part I. A study of prevalence. *Br J Psychiatry* 1964; 110:146-158.

3. Elliot J: Care for the demented: It may be up to the family. *JAMA* 1979;241:231.

4. Hachinski V, Lassen N, Marshall J: Multi-infarct dementia: A cause of mental deterioration in the elderly. *Lancet* 1974;2:207-210.

5. Bergmann K, Kay DWK, Foster E, et al: A follow-up study of randomly selected community residents to assess the effects of chronic brain syndrome and cerebrovascular disease, in de la Fuente R, Weisman MN (eds): *Psychiatry: Proceedings of the Fifth World Congress of Psychiatry*. Amsterdam, Excerpta Medica, 1973, pp 884-885.

6. Goldstein K: The effect of brain damage on the personality. *Psychiatry* 1952;15:245-260.

7. Lowenthal M: *Lives in Distress*. New York, Basic Books Inc, 1964, pp 87-98.

8. Grad J, Sainsbury P: Mental illness and the family. *Lancet* 1963;1:544-547.

9. Sanford J: Tolerance of disability in elderly dependents by supporters at home: Its significance for hospital practice. *Br Med J* 1975; 2:471-473.

10. Parkes M: The first year of bereavement. *Psychiatry* 1970;33:444-467.

11. Bergmann K, Foster E, Justice A, et al: Management of the demented elderly in the community. *Br J Psychiatry* 1978;132:441-449.

12. Zarit SH, Reever KE, Bach-Peterson J: Relatives of the impaired elderly: Correlates of feelings of burden. *Gerontology* 1980;20:649-655.

13. Caplan G: Mastery of stress: Psychosocial aspects. *Am J Psychiatry* 1981;138:413-420.

14. Dunlop B: Expanded home-based care for the impaired elderly: Solution or pipe dream? *Am J Public Health* 1980;70:515-519.

15. Rabins P: Management of irreversible dementia. *Psychosomatics* 1981;22:591-597.

16. National Institute on Aging Task Force: Senility reconsidered: Treatment possibilities for mental impairment in the elderly. *JAMA* 1980;244:259-263.

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Senator GRASSLEY. Dr. Damasio?

Dr. DAMASIO. Mr. Chairman, I am pleased to testify today, both as a neurologist who cares for a significant number of new patients with Alzheimer's disease every year, and also as a neurological scientist dedicated to the understanding of brain disease, and especially Alzheimer's disease.

The witnesses who have preceded me reviewed quite extensively the panorama of Alzheimer's disease today: the tragedy of these patients and their families, the staggering social and personal losses subsequent to the disease, and the positive new achievements in science, related to Alzheimer's disease especially in the past 5 last years.

Let me just summarize some of the points that I would like to make. One is that, if anything, the estimates of the magnitude of the problem that you have heard this morning are, in my view, conservative. I think that as heart disease and stroke decline as primary health problems in the Nation, as infectious diseases are more controllable, and cancer is better handled, Alzheimer's disease is going to become more and more prominent as a health problem. Patients are going to have longer survival times, are going to become more vulnerable to this disease, and it is certainly going to stand out in statistics by the end of this century, much more than it does today. I will not review the very important evidence that speaks to the fact that Alzheimer's disease is indeed a killer in this Nation, even if it does not figure in death certificates all the time.

There has been immense progress in the past decade. However, I think it is just as important to emphasize the strides we have made and the fact that we have very important new leads in this disease, as it is to emphasize, with some modesty, what we really do not know. And I think that our knowledge in Alzheimer's disease is deficient in almost every aspect. For instance, the epidemiological knowledge that we have been quoting this morning is, of course, better than the one we had 10 years ago, but it is still insufficient. We need to know in detail, for instance, which types of population are at risk for Alzheimer's disease, and we do not know that. We need to know which ones are at greater risk—for instance, it is possible that we may find that certain risk factors in, say, the environment, or in special occupations or lifestyles, or even in specific genetic pools, may have a bearing on this disease. We have, considerable knowledge on the neuropathology of Alzheimer's disease, but we still do not know about the fine neuroanatomy of the disease. That has not been elucidated. Needless to say, the neurochemistry, neuropharmacology, and the neuroimmunology of this disease are just in its infancy.

I think our goal at this point, is to understand the disease in its broad terms. We need to understand its cause or causes. We need to understand the mechanisms of production of the disease, and we need to understand its intimate course. This is the only way in which we may be able to prevent the disease or abort it once it starts, and that is obviously our ultimate goal, to prevent and the disease or to abort it in those that have already acquired it. And as to the means to achieve those goals, I would say very briefly that we need to promote a comprehensive program of fundamental research, by which I mean that we have to have a program that ap-

proaches in a very comprehensive and basic way what the disease is, in its neurological terms. I do not think that I would single out a specific approach. I do not think we can predict which particular approach within neuroscience is going to reveal the clue to the cause and to the course of the disease. We need to be very open. We need to engage practically all of the neurosciences as we know them today. We definitely have to approach the problem, both in humans, in patients who have the disease, in what is traditionally known as "clinical science," and also through "basic science", for instance, in pertinent laboratory research animals. The possible frontiers and the possible solution are likely to be in such areas as neurogenetics or neuroimmunology. But we definitely need to make use of all the spectacular improvement in diagnostic means of studying the brain, for instance, in the field of neuroimaging. This was mentioned by Dr. Murray Goldstein in relation to the PET scanner, and other means of neuroimaging such as single-photon emission tomography SPECR, CT-scan, and, nuclear magnetic resonance, can be used to further the understanding of this disease.

I do not think that the problem is easy at all. I think it is a very complex problem to approach; but I believe it is quite possible that if a major, comprehensive research effort is directed at Alzheimer's disease, we will find a way of preventing and ameliorating this illness. If we fail to do that, if we do not have support for that major scientific effort, I think that Alzheimer's disease will be, by the end of this century, a really unsurmountable health problem and social problem.

Thank you very much.

[The prepared statement of Dr. Damasio follows:]

Testimony to the Committee on Labor and Human Resources

Subcommittee on Aging

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To many physicians the diagnosis of dementia means the identification of progressive mental deterioration, accompanied by progressive motor incapacity, leading to early loss of independence, complete disability and early death. Whether dealing with so-called senile dementias, or with those with onset in the fifth or sixth decades, physicians have conceived of the underlying process as one of either natural or premature aging of the brain. As for treatment, the entrenched idea has been that there is nothing to offer and that the fatal course is not modifiable by therapy. The concept that dementia is a single and untreatable pathologic entity has dominated medical thinking until recently.

But in the past decade this concept has been changing significantly and we hope it will change more radically in the 1980's. Three factors have contributed to the modification in attitude. Firstly, is a realization the term dementia is a merely descriptive one, which does not denote a disease entity and does not hallmark an irreversible process. Secondly, is the evidence that many demential syndromes are treatable. Thirdly, is the realization, only now beginning, that dementia is not a symptom of aging, that the demential syndromes are manifestations of a complex of diseases which all adults may develop although older adults are at a greater risk, and that a major research effort can actually lead to the prevention or treatment of most of those diseases.

It has become obvious that the term dementia merely designates the presence of acquired and progressive impairment of intellectual and affective abilities. But the term does not have any neuropathologic implication whatsoever, should not be equated with a single disease, and should not be taken as a synonym of helpless fate since the clinical label does not relate to the outcome. Nor does the label refer to a uniform cluster of signs and symptoms. A wide variety of clinically distinctive demential syndromes may be individualized if close attention is paid to the mode of onset of the early signs, to their subsequent rate of development and to their interrelations, and indeed more needs to be known in this regard. The objective detection of dementia, generally made on the basis of a single observation at some point in the clinical course, does not by itself reflect the previous evolution of the syndrome and has, by itself, little predictive value. The designation <u>demential syndrome</u> should really be favored over that of <u>dementia</u> It should be understood that there are a variety of clinical presentations and pathologic origins.

Of all the demential syndromes those that have a degenerative origin are the most frequent (more than 50% in any series) and least amenable to therapy. The principal entity in the group is Alzheimer's disease. The major neuropathologic features include atrophy of certain brain areas, caused by the loss of neurons in those areas and the presence of neurofibrillary tangles, granulovacuolar changes and senile plaques. In the view of modern researchers, this is disease entity proper, one in which the intensity of the histological picture correlates fairly well with the behavioral devastation seen by clinicians and lay people alike. It is imperative to distinguish the intellectual decay of Alzheimer's disease from the benign memory loss of the aged.

The human and social costs of Alzheimer's disease are difficult to calculate, but are, without a doubt, staggering. The fact that Alzheimer's is a disease which kills or helps to kill its carrier further increases the toll. Though our knowledge of this epidemiologic point is sparse there is little doubt that the survival of a patient with Alzheimer's is significantly lower than that of a nonaffected subject of the same age. The average survival of a patient with Alzheimer's is 2.6 years for males and 2.3 for females. The average surival of non-affected population of comparable age is, respectively, 8.7 and 10.9 years. Even the more optimistic studies, agree that life expectancy after the onset of Alzheimer's dementia is reduced by at least half. Whether by itself, or by fostering the appearance of associated conditions, such as pulmonary infection or embolism, Alzheimer's disease <u>is</u> a killer.

The overall prevalence of Alzheimer's disease in the population over age 65 is about 15%. Because that segment of the population increases constantly the incidence is likely to rise to astonishing values. At any given moment, more than 1 million Americans suffer from Alzheimer's. That amazing figure does not include other dementias on a degenerative basis, such as those accompanying Huntington's disease, the cerebellar degenerations or some extrapyramidal syndromes. The figure also does not include another major cause of "non-treatable" dementia, multiple infarction of the central nervous system, related to cardiovascular disorders, especially disease of the neck vessels and systemic hypertension.

The solution of the problem of the degenerative dementias will come only as the result of a major investigative effort. A fundamental science approach, in both animals and humans is essential, in our view, if the problem is to be attacked properly. Mere application of currently

available knowledge, although necessary and even mandatory, simply will not do.

Our knowledge is deficient in almost every aspect that relates to Alzheimer's disease. The epidemiological knowledge is insufficient. We need to know in detail which types of population are at risk for Alzheimer's disease, or, if all are at risk, which ones are at a greater risk. It is possible that we may find out about risk factors related to the environment, to special occupations, to life styles, or to special genetic pools. The association between Alzheimer's disease and other diseases needs to be explored further (for instance, an association with leukemia and with the Down Syndrome has been recently recognized). While considerable knowledge has been obtained in the neuropathology of Alzheimer's, the fine neuroanatomy of the disease has not been elucidated. For instance, the distribution of senile plaques is anything but diffuse or random throughout the brain. Structures of the limbic system and of major association cortices suffer the brunt of the damage. But more needs to be known about specific subsets of those anatomic structures in their relation to the disease. Because different structures of the brain have different vulnerability to different pathological causes, the differential involvement of such structures as the hippocampus or the the basal forebrain (which includes the nucleus basalis of Meynert) will tell us much about both the mechanisms of causation of symptoms and about the mechanism of acquisition of the disease. Needless to say, the elucidation of the neurochemical and neuropharmacological aspects of the illness is crucial and its approach is its infancy.

Clearly, a variety of avenues will be necessary to increase our understanding of Alzheimer's disease and lead to the prevention or amelioration of the condition. But if we were asked to assign priorities to the several means of attaining that goal we would say: Let us first, without delay, attempt to discover the mechanisms of the disease so as to be able to prevent it or block its progression. Let us, in the meantime, improve the clinical neurological diagnosis so as to provide the most rapid and effective detection of the disease, distinguish it from instances of dementia which are immediately amenable to treatment, and learn as much as we can about the epidemiology of the disease. That end in itself should be readily achievable as it depends on the proper coordination of a variety of recent developments in the fields of neurology and imaging of the brain. Finally, let us maintain the social and medical support services that will be necessary to help both patients and families bear the consequences of the disease with the least possible suffering.

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Senator GRASSLEY. Thanks, once again, to all of you. I probably have more questions than we can take time to ask right now, but I want to get a few of them in, and then we will probably write to you and ask you to respond to the rest in writing, if you would.

First of all, Dr. Reisberg, in regard to the drug, naloxone, I wanted to ask you if the article that was in the Washington Post March 24, headlined, "Drug Found To Be Promising in Alzheimer's Disease"–is that an apt characterization of what you know about research on the drug to this point?

Dr. REISBERG. We have very preliminary observations for which relate to the effects of naloxone in patients with Alzheimer's disease. At this time, I would say that the investigations, which we recorded in March in the New England Journal of Medicine now apply to nine patients as opposed to the seven patients at that time, and they remain at least as promising as they were in March. Now, those investigations related primarily to the short-term effects of this substance. We had some long-term effects on family members, but we do not know if those long-term effects were a long-term carryover in the family member of the short-term effect on the patient, or were truly long-term effects on the patient. We need to study the duration of the effects of this compound in patients with Alzheimer's disease. We need to study further what kinds of patients respond in terms of the stages of the evolution of the illness. We need to study further dose-response relationships with respect to the response. We need to begin by, certainly, replicating with larger numbers of subjects our initial preliminary findings. Finally, there are oral analogues of this compound, naloxone. One which is somewhat well-known naltrexone, and hence, it might be possible this treatment, if indeed it proves to be such, might point the way to an orally effective treatment or remediation of the disorder, and oral analogues of this compound need to be studied, as do other compounds which exert similar effects on the brain's chemistry. Hence, those observations are very preliminary, and I do believe that with further research, we will be able to say a great deal more about them.

Senator GRASSLEY. Getting consent to participate in the experiments, naturally, would be difficult because the mental capacity of the participant might not constitute informed consent. Have you had any difficulty overcoming that problem?

Dr. REISBERG. A few things of relevance happen in the Alzheimer's patient. I might mention that the Institutes did hold a conference about a year and a half ago, with respect to legal and ethical issues in relationship to informed consent in the Alzheimer's patient, and I did attend that conference. We perceive it in several ways. In all cases, when patients are impaired, we get the consent not only of the patient participating in our program, but also the family member who is responsible for the care of that person as well. It is only when we get the consent of both the patient and the accompanying family member that we proceed with our investigations. In a practical sense, that is the mechanism by which we proceed with studies in this area.

There is another aspect which relates somewhat to what Nancy Mace was saying with regard to some of the changes in the Alzheimer's patient as the illness evolves. That is, the loss of a mind is

a terrible, terrible, terrible loss, and with any major loss, the loss of a loved one, or the loss of a limb, we react as human beings with a psychological process known as "denial." Similarly, the loss of a mind is too terrible a loss for conscious contemplation, and hence, if you ask a person as this illness evolves, "Do you have a memory problem?" they will frequently say "No" and the more specifically you ask that question, the more likely you are to get an answer of "No." They cannot face up to this terrible loss. And hence, we obtain the permission of patients for treatment of a memory problem even though they will not directly admit that they suffer from such a problem, and denial is a major aspect of this illness, and it is one that has to be dealt with with respect to issues of informed consent in general.

Senator GRASSLEY. Nancy, have you seen a trend toward relatives "dumping" their relatives who have Alzheimer's disease in nursing homes?

Ms. MACE. Absolutely not. They keep them at home as long as they possibly can. It was originally assumed that the reason for placement was because the patient's condition deteriorated. What we are seeing is that families place patients because the caregiver eventually got sick, more often than not.

But no, families are keeping these people at home as long as they possibly can, at enormous costs to themselves physically, financially, and emotionally. What we do see is caregivers who are completely burned out by the task of care.

Senator GRASSLEY. Has your service ever recommended putting somebody in a nursing home?

Ms. MACE. We let families know that we will support them and their decision, in sorting out what is right for them, and we try to help them sort through what needs to be done. If a caregiver himself or herself becomes very ill, they may not have any choice, and then we will stand by them in that. We try to work very individually with families.

Senator GRASSLEY. You mentioned that nursing homes sometimes refuse to take patients with this disease. Has that got anything to do with whether or not they are qualified to do it? Are they equipped to take care of these people?

Ms. MACE. Nursing homes provide very different kinds of care, depending on the facility. Some nursing homes are taking these patients and are doing very, very well with them. I have visited many nursing homes which have asked for our help in teaching their staff more about how to manage these patients. In general, I would say that nursing homes need and seek more information about how to take care of Alzheimer patients. They themselves feel that they could do better in the management of these people. They can be very difficult patients. A person who is mobile and cannot think is hard in any setting.

Senator GRASSLEY. The yoking of medicare and private health insurance created a problem to the extent that people cannot get the help they need in their own homes?

Ms. MACE. Yes; I think that is an issue. People cannot get the financial help that they need to at least partially pay the cost of care at home, particularly when they do not need skilled nursing care. These patients more often need personal care and supportive

care and somebody to help out, and that kind of care is most often not paid for. Families need that financial assistance.

Senator GRASSLEY. Dr. Damasio, everybody else has been very cautious about talking about the hereditary aspects, if any, of the disease. What are your feelings about that?

Dr. DAMASIO. I think one should be cautious, indeed. There is no doubt that there is a sizable number of patients with Alzheimer's disease that have a hereditary pattern. You can find families in which a sizable number of subjects are struck with Alzheimer's disease. That is, however, in my view, a minority of patients. I believe the majority of patients with Alzheimer's disease do not have a relative with Alzheimer's disease. But this does not mean that—although we can exclude or minimize the risk of transmission.

Senator GRASSLEY. Since you are with the University of Iowa College of Medicine, I wanted to ask you about a referral of statistics that Ms. Mace gave in her testimony about a Rand Corp. study in 1981 that indicates that by 1990, we will need between 7,000 and 10,300 geriatricians. Are our medical schools up to the task of providing those?

You know, back when I was in the State legislature, we used to have an institute on gerontology at the University of Iowa, and then it was eliminated. I guess we did not think we were ever going to get any older than what we were then.

Dr. DAMASIO. I think there is more and more awareness——

Senator GRASSLEY. That institute is not back, is it? It was eliminated in the early seventies.

Dr. DAMASIO. As an institute, I do not think it is back. But there is a very large number of members of the faculty, of physicians in general, and an extensive number of professionals in the aging network; namely, in the gerontology project at the school of social work, who are very, very aware of the problems of Alzheimer's disease and of other dementias—Alzheimer's disease is, of course, only one of the dementias that is plaguing the elderly.

As to the medical schools, I know that our medical schools, the aging curriculum has been increased, and there are a number of courses throughout the school which aging—which emphasize the problems of the elderly, not only in relation to its neurological aspects, but also the internal medicine, psychiatric, and very especially the social issues related to the elderly. So I think that our school is certainly aware of the problem in increasing its curriculum, and I think that this is happening in other medical schools as well.

Senator GRASSLEY. Are there standard courses for medical students in this area?

Dr. DAMASIO. In several of the courses, there are specific lectures that address the problem. For instance, the issue of Alzheimer's disease is raised from the first year of medical school, and very strongly attacked in the third and fourth year curriculum at our school.

Senator GRASSLEY. Would that be true of most of the hundred or so medical schools that we have, or are you talking about just a few?

Dr. DAMASIO. I do not think I would be able to comment on that.

Senator GRASSLEY. But at the University of Iowa, this is applicable.

Dr. DAMASIO. Oh, yes.

Senator GRASSLEY. Maybe I ought to ask you, then, were you speaking specifically about the University of Iowa, or——

Dr. DAMASIO. I was specifically referring to the University of Iowa when I referred to the lectures in the curriculum.

Senator GRASSLEY. Could you comment on that, Dr. Reisberg?

Dr. REISBERG. This is an illness which everyone is literally learning about at the same moment. Doctors at this point are literally as ignorant about this illness as laymen. I get telephone calls from physicians who tell me that they have patients who come to them with what they call Alzheimer's disease, but they really think it is arteriosclerosis, and what should they do with them.

I am a member of a committee to develop a curriculum in geriatric psychiatry, which is only now meeting for the first time with respect to the psychiatric aspects of this illness.

With respect, I would say, to all other medical specialties, doctors and other professionals are learning about this illness even as the lay public learns about the illness. The lay public began to hear the name, "Alzheimer's disease,"last November. The vast majority of the medical profession began to hear of Alzheimer's disease as not an exotic illness, but as a major illness, in November of 1982. The lay public read about the first cases of Alzheimer's disease in January of 1983. The medical profession became aware of what Alzheimer's disease looks like for the first time in January of 1983. The lay public became aware in March of 1983 that investigators were working on effective treatments for this disorder. The medical profession became aware that investigators were working on effective treatments for this disorder somewhat earlier in this case, because there was a lot of medical publicity attached to the early attempts at cholinergic intervention.

But for the most part, ignorance of this illness has extended to all levels of our society. I come from New York, and at the same moment that you are holding Senate hearings, I was contacted a few days ago with respect to State testimony on this illness. City hall in New York held a conference on this illness for the first time last November and is planning a major conference for next November.

I believe that just as all areas of government are learning about this illness at the same moment, so all areas of medicine are learning about this illness at the same moment.

Senator GRASSLEY. Well, I think that that is a good place for me to quit my questions, because I think that your remarks, Dr. Reisberg, tell us we have a long way to go, and it is going to take a lot of cooperation among different levels of government and different groups, and that we must start by learning more ourselves. That is the vein in which this hearing was held, and I look forward to continuing the record and the activity so that we might draw greater public attention to this disease.

I want to thank you, as well as all witnesses, for appearing here today and for helping to create a record that I hope will be very valuable.

At this point, I order printed all statements of those who could not attend and other pertinent material submitted for the record.

[The material referred to follows:]

May 12, 1983

Statement

Reynold Spector, M.D.
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Alzheimer's Dementia - a disease of unknown cause in which a patient loses his/her mental powers; there is no effective treatment.

I speak from my perspective as a Director of both a Division of General Internal Medicine (which includes a Section of Geriatrics) and a Division of Clinical Pharmacology in a large University hospital.

I believe that the current projections of the magnitude of the problems of dementia and the decline of cerebral function in the elderly are serious underestimates. Part of the reason for my belief is that many of the more traditional diseases (in large part because of great advances in medical science) will become relatively less important causes of morbidity and mortality in future years. For example, for the first time in 1982, according to the United States Public Health Service, cardiovascular diseases were no longer the leading cause of premature mortality in the United States. The decline in cardiovascular mortality has been occurring for some years. For these and other reasons, I foresee increasing numbers of elderly patients with problems of declining cerebral function and dementia.

In a geriatrics section of a general Internal Medicine unit, the principal problem is the elderly patient with an untreatable decline in cerebral function. These patients are extremely difficult to manage, are an enormous burden to society and are heart-rending, tragic experiences for the involved families.

At the present time, it seems to me that the United States should support basic and clinical research in dementia and related disorders with a very high priority. I believe that an investment in basic and clinical research in the central nervous system will yield long term rewards, e.g., a better life for the elderly and substantially lower costs to society. I believe that funds spent on social programs that aid in the care of such patients, although important, will not achieve any fundamental understanding. Without scientific knowledge of these disorders, prevention and/or effective treatment are unlikely. In my view, there are a sufficient number of well-trained neuroscientists and others who are interested in basic and clinical research in the central nervous system. I believe such investigators should be supported within the limits of efficient research.

There are two problems for basic and clinical research in the central nervous system at this time. First, there are able neuroscientists in the United States who are under-funded in terms of their ability to carry out meaningful research. These investigators, with excellent training, deserve more adequate funding to aid in the conquest of the dementing and related disorders. Second, there is a significant problem in doing research on demented patients. That problem has to do with the issue of informed consent which, almost by definition, cannot be given by a demented patient. Without informed consent, the investigator, at present, is unable to perform certain types of important research. In order to do meaningful research on demented patients, some mechanism needs to be evolved that will allow ethical and conscientious clinical investigators to do clinical research in demented patients. This is a very difficult problem, but one which is outstanding and requires a solution.

Finally, I would say that there is some substantial hope in the future for the investigation, prevention, and/or treatment of the dementing and related illnesses. The revolution in molecular biology has opened up many, new, possible research areas that can and should be pursued. With proper support and the control of Eris, I foresee tremendous gains in knowledge. Armed with fundamental scientific knowledge, prevention and treatment will emerge.

Senator GRASSLEY. At that point, I will say this hearing is adjourned, and thank you very much.

[Whereupon, at 12:30 p.m., the subcommittee was adjourned.]

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